IFW

UNITED STATES PATENT AND TRADEMARK OFFICE

OIPE
FEB 28 2007
PATENT & TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/678,767	10/03/2003	Srinivas G. Rao	CYPR 105/108	3411

7590 02/20/2007

Srinivas G. Rao
11590 Jaguar Court
San Diego, CA 92131

EXAMINER	
HUYNH, CARLIC K	
ART UNIT	**PAPER NUMBER**
1617	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/20/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

OIPE
FEB 28 2007
PATENT & TRADEMARK OFFICE

Office Action Summary	**Application No.** 10/678,767	**Applicant(s)** RAO ET AL.	
	Examiner Carlic K. Huynh	**Art Unit** 1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 November 2006*.
2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.
3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.
4a) Of the above claim(s) *4,5 and 22-28* is/are withdrawn from consideration.
5)☐ Claim(s) _____ is/are allowed.
6)☒ Claim(s) *1-3 and 6-21* is/are rejected.
7)☐ Claim(s) _____ is/are objected to.
8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.
10)☒ The drawing(s) filed on *03 October 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a)☐ All b)☐ Some * c)☐ None of:
1.☐ Certified copies of the priority documents have been received.
2.☐ Certified copies of the priority documents have been received in Application No. _____.
3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

U.S. Patent and Trademark Office
PTOL-326 (Rev. 08-06) **Office Action Summary** Part of Paper No./Mail Date 20070201

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date : 02 March 2004, 29 July 2004, and 24 August 2005.

DETAILED ACTION

Status of the Claims

1. Claims 1-28 are pending in the application, with claims 22-28 having been withdrawn from consideration, in response to the restriction requirement submitted on October 20, 2006. Accordingly, claims 1-3 and 6-21 are being examined on the merits herein.

Election/Restrictions

2. Applicant's election without traverse of the claims of Group I, namely claims 1-21, in the reply filed on November 16, 2006 is acknowledged.

Claims 22-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on November 16, 2006.

Additionally, Applicant's election without traverse of fibromyalgia syndrome (FMS) as the species of chronic neurological disorder and milnacipran as the species of antidepressant, in the reply filed on November 16, 2006 is acknowledged.

Claims 4-5 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on November 16, 2006.

The election/restriction requirement is deemed proper and is made FINAL.

Information Disclosure Statement

3. The Information Disclosure Statement submitted on March 2, 2004, July 29, 2004, and August 24, 2005 is acknowledged.

Drawings

4. The drawings are objected to because of a typographical error in the title label of Figure 3. The title label of Figure 3 shoud be "Beck Scores". Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

5. The drawings are objected to under 37 CFR 1.83(a) because figure 1 fails to show clearly the dosing schedule of the "treatment protocol" as described in the specification (page 20, line 8). Figure 1 is of poor print quality that hinders the ability of any one skilled in the art from interpreting properly. Any structural detail that is essential for a proper understanding of the

disclosed invention should be shown in the drawing. MPEP § 608.02(d). Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-2, 6-8, 10-17, and 19-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for fibromyalgia syndrome (FMS) and milnacipran, does not reasonably provide enablement for chronic neurological disorders and

antidepressants. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547, the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1). ***Nature of the Invention***:

The rejected claim(s) is/are drawn to an invention which pertains to a method of treating symptoms of a chronic neurological disorder or pain associated therewith in a patient in need of treatment comprising: administering an antidepressant in an escalating dosage over a period of time until a maintenance dosage is reached.

(2). ***State of the Prior Art***:

The skilled artisan would treat a chronic neurological disorder with an antidepressant.

(3). ***Relative Skill of Those in the Art***:

The relative skill of those in the arts of chronic neurological disorders and antidepressants is extremely high.

(4). ***Predictability of the Art***:

The treatment of any chronic neurological disorder comprising administering any antidepressant is highly unpredictable. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and that physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(5). ***Breadth of the Claims***:

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass the administration of any antidepressant as a treatment for any chronic neurological disorder.

(6). ***Direction or Guidance Presented***:

The guidance given by the specification as to the method for treating a chronic neurological disorder comprising administrating an antidepressant of the instant invention is limited.

The disclosure of the method of treating fibromyalgia syndrome (FMS) comprising administering milnacipran is adequate (page 7, lines 1-5; page 11, lines 17-20; and page 28, lines

23-29).

(7). ***Working Examples***:

For treatment of fibromyalgia syndrome (FMS) comprising administering a dosing escalation of milnacipran, the working examples in the specification show improvement in tolerance at the 200 mg/day dosage in patients treated initially at 100 mg/day escalating up to 200 mg/day than in patients treated at the 200 mg/day dosage from the onset (page 30, lines 15-17) as well as in tolerance and in the alleviation of pain symptoms of twice a day dosing than once a day dosing (page 35, lines 18-23). Thus, the working examples show how to treat fibromyalgia syndrome (FMS) comprising administering milnacipran, not how to treat any chronic neurological disorder comprising administering any antidepressant.

Note that lack of a working example to treat any chronic neurological disorder comprising administering any antidepressant, is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP 2164.

(8). ***Quantity of Experimentation Necessary***:

The specification fails to provide sufficient support of treating any chronic neurological disorder comprising admistering any antidepressant. As a result, one of skill in the art would be forced to perform an exhaustive search for the embodiments of any drugs having the function recited in the instant claim suitable to practice the claimed invention.

Therefore, in view of the Wands factors, e.g. the predictability of the art, the amount of direction or guidence, and the lack of working examples discussed above, a person of skill in the art would not be able to fully practice the instant invention without ***undue experimentation***.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

7. Claims 1-3 and 6-21 are rejected under 35 U.S.C. 102(a) as being anticipated by Kranzler and Rao (U.S. Patent 6,635,675).

Kranzler and Rao teach treating a chronic neurological disorder or pain, e.g. fibromyalgia syndrome (FMS) or chronic fatigue syndrome (abstract).

Kranzler and Rao also teach milnacipran is a serotonin norepinephrine reuptake inhibitor (column 3, lines 41-46), an analgesic (column 7, lines 30-31), an NMDA receptor antagonist (column 7, lines 6-7), is non-toxic in humans (column 6, lines 24-28), is manufactured in a sustained release form (column 10, 35-36), and is administered in an escalating dosage (column 14, lines 55-59).

Kranzler and Rao also teach a kit with instructions teaching a method of using milnacipran (column 3, lines 14-17).

Regarding claim 16, "patient safety profile" and "peak plasma concentration" are inherent properties. Since Kranzler and Rao teach milnacipran, used as an antidepressant, is non-toxic in humans, it is reasonably expected that such a compound would yield a positive patient safety profile and a suitable peak plasma concentration as recited in claim 16.

For these reasons the claimed subject matter is deemed to fail to patentably distinguish over the state of the art as represented by the cited reference. The claims are therefore properly rejected under 35 U.S.C. 102 (a).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-3, 6-10, 14-16, and 19-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koppel (U.S. Patent Application No. 2004/0014739) in view of Spencer et al. (Drugs, 1998, 56, 405-427) and Kranzler et al. (Psychopharmacology Bulletin, 2002, 36, 165-213).

Koppel teaches the anti-depressant N-acetylated-α-linked acidic peptidase or NAALADases (page 1, paragraph [0004]), its use to treat depression, pain, circadian rhythm disorder (page 6, paragraph [0107]), Attention-Deficit Hyperactivity Disorder (ADHD), and Post-traumatic Stress Disorder (pages 6-7, paragraph [0108]).

Koppel also teaches a prolonged release dosage form (page 11, paragraph [0128]).

Koppel does not teach milnacipran as an antidepressant, dose escalation of milnacipran, milnacipran is a norepinephrine serotonin reuptake inhibitor (NSRI), milnacipran is well tolerated in human patients, pain relief (analgesia) associated with milnacipran, milnacipran is an NMDA inhibitor, and milnacipran as a treatment with fibromyalgia syndrome (FMS).

Spencer et al. teach milnacipran is used to treat depression (p. 408), the treatment of depression using dose escalation of milnacipran (p. 409), milnacipran is a norepinephrine serotonin reuptake inhibitor (p. 406), and milnacipran is well tolerated in human patients (p. 409).

Kranzler et al. teach N-methyl-D-aspartate (NMDA) receptors are in the pain processing pathway and that inhibitors of NMDA can reduce pain and are analgesic (pp. 170-171).

Kranzler et al. also teach the antidepressant milnacipran exhibits mild NMDA inhibition (p. 190).

Furthermore, Kranzler et al. teach antidepressants are a common form of therapy for many chronic pain states, including FMS (p. 186).

To a person of skill in the art at the time of the invention, it would have been obvious to employ the antidepressant NAALADase of Koppel to treat depression because the compounds of Spencer et al. and Kranzler et al. are antidepressants and analgesics and according to Spencer et al. and Kranzler et al., milnacipran treats depression as well as pain associated with FMS.

The motivation to combine the compounds of Koppel to the compounds of Spencer et al. and Kranzler et al. is that the compounds of Spencer et al. and Kranzler et al. are antidepressants and analgesics and that such antidepressants and analgesics treat depression as well as pain associated with FMS.

Regarding claim 16, "patient safety profile" and "peak plasma concentration" are inherent properties. Since Spencer et al. teach milnacipran, used as an antidepressant, is well tolerated in human patients, it is reasonably expected that such a compound would yield a positive patient safety profile and a suitable peak plasma concentration as recited in claim 16.

9. Claims 1, 17-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koppel (U.S. Patent Application No. 2004/0014739) in view of Kranzler et al. (U.S. Patent 6,635,675).

The teachings of Koppel are summarized above.

Koppel does not teach a dose pack containing instructions for administering milnacipran for the treatment of a chronic neurological disorder such as fibromyalgia syndrome (FMS).

Kranzler et al. teach a kit comprising milnacipran packaged in association with instructions teaching a method of using milnacipran.

To a person of skill in the art at the time of the invention, it would have been obvious to employ the antidepressant NAALADase of Koppel to treat depression because the kit of Kranzler et al. contain antidepressants and analgesics and according to Kranzler et al., milnacipran treats depression as well as pain associated with FMS.

The motivation to combine the compounds of Koppel to the compounds of Kranzler et al. is that the compounds of Kranzler et al. are antidepressants and that such antidepressants treat depression as well as pain associated with FMS.

Double Patenting

Obviousness-Type

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 1 and 9 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Hirsh et al. (U.S. Patent Application No. 2006/0024366) and claim 1 of copending Hirsh et al. (U.S. Patent Application No. 2004/0132826). Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 1 of each of the Hirsh et al. applications is directed at a milnacipran formulation, which is the same milnacipran used in a method for treating a chronic neurological disorder in the instant claims 1 and 9. Thus the milnacipran formulation is not patentably distinct between each of the Hirsh et al. applications and the instant application.

This is a provisional double patenting rejection since the conflicting claims have not been patented.

11. Claims 1 and 9 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of Kranzler et al. (U.S. Patent 6,635,675), claim 1 of Kranzler et al. (U.S. Patent 6,602,911), and claim 1 of Kranzler et al. (U.S. Patent 6.992,110)

in view of Koppel (U.S. Patent Application No. 2004/0014739), Spencer et al. (Drugs, 1998, 56, 405-427) and Kranzler et al. (Psychopharmacology Bulletin, 2002, 36, 165-213) as applied to claims 1-3, 6-10, 14-16, and 19-21 above.

12. Claims 1 and 9 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 76, 82, 84, 88, 90, and 94-95 of copending Application Kranzler et al. (US 2004/0019116), claims 1, 3, 27, and 30 of copending Application Kranzler et al. (US 2003/0232805), claim 1 of copending Application Rao et al. (US 2003/0203055), claim 1 of copending Application Rao et al. (US 2005/0096395), claims 1, 14, and 20 of copending Application Rao et al. (US 2004/0034101), claims 1, 2, 8, 11-12, and 18 of copending Application Rao et al. (Serial No. 11/535,237), claims 1 and 3 of copending Application Rao et al. (US 2005/0032782), and claim 177 of copending Application Anderson et al. (US 2007/0021352) in view of Koppel (U.S. Patent Application No. 2004/0014739), Spencer et al. (Drugs, 1998, 56, 405-427) and Kranzler et al. (Psychopharmacology Bulletin, 2002, 36, 165-213) as applied to claims 1-3, 6-10, 14-16, and 19-21 above.

This is a provisional double patenting rejection since the conflicting claims have not been patented.

13. Claims 1 and 9 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 35, 38, and 40 of copending Application Rao et al. (US 2006/0039866) and claims 35 and 40 of copending Application Rao et al. (US 2006/00398867) in view of Koppel (U.S. Patent Application No. 2004/0014739), Spencer et al. (Drugs, 1998, 56, 405-427) and Kranzler et al. (Psychopharmacology Bulletin, 2002, 36, 165-213) as applied to claims 1-3, 6-10, 14-16, and 19-21 above.

Furthermore, Kranzler et al. teach nonrestorative sleep is a common problem in patients with FMS (p 180).

This is a provisional double patenting rejection since the conflicting claims have not been patented.

Conclusion

14. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carlic K. Huynh whose telephone number is 571-272-5574. The examiner can normally be reached on Monday to Friday, 8:30AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ckh

S. Wang

SHENGJUN WANG
PRIMARY EXAMINER

Please type a plus sign (+) inside this box → ☐

PTO/SB/08A (10-96
Approved for use through 10/31/99. OMB 0651-0031
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

OIPE
FEB 2 8 2007
IAP08
PATENT & TRADEMARK OFFICE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number

OIPE
JC16
MAR 0 2 2004
PATENT & TRADEMARK OFFICE

Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Complete if Known	
Application Number	10/678,767
Filing Date	October 3, 2003
First Named Inventor	Srinivas G. Rao
Group Art Unit	
Examiner Name	
Attorney Docket Number	CYPR 105/108

Sheet 1 of 15

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	US Patent Document Number	Kind Code[2] (if known)	Name of Patentee or Applicant of Cited Document	Date of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
CA		3,948,254		Zaffaroni	04-06-1976	
CA		3,977,992		Hofacker	08-31-1976	
CA		4,069,307		Higuchi, et al.	01-17-1978	
CA		4,093,709		Choi, et al.	06-06-1978	
CA		4,122,157		Huber	10-24-1978	
CA		4,138,475		McAinsh, et al.	02-06-1979	
CA		4,142,526		Zaffaroni	03-06-1979	
CA		4,173,626		Dempski	11-06-1979	
CA		4,226,849		Schor	10-07-1980	
CA		4,249,531		Heller, et al.	02-10-1981	
CA		4,252,786		Weiss, et al.	02-24-1981	
CA		4,264,573		Powell, et al.	04-28-1981	
CA		4,304,232		Michaels	12-08-1981	
CA		4,308,251		Dunn, et al.	12-29-1981	
CA		4,322,311		Lim, et al.	05-30-1982	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Office[3]	Number[4]	Kind Code[5] (if known)	Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
CA		PCT	WO 95/22521		Asahi Chemical Ind.	08-24-1995		
CA		PCT	WO 97/33880		Eli Lilly and Co.	09-18-1997		
CA		PCT	WO 00/28980		Eli Lilly and Co.	05-25-2000		
CA		PCT	WO 01/26623		Laxdale Ltd.	04-19-2001		
CA		PCT	WO 02/060428		Sepracor, Inc.	08-08-2002		

Examine Signature	Carlos Azpuru	Date Considered	1/24/07

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to application.

[1] Unique citation designation number [2] See attached Kinds of U.S. Patent Documents. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant to place a check mark here if English language Translation is attached.

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SENT TO: Assistant Commission for Patent, Washington, DC 20231.

Please type a plus sign (+) inside this box → ☐

PTO/SB/08A (10-96
Approved for use through 10/31/99. OMB 0651-0031
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number

Substitute for form 1449A/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (use as many sheets as necessary)				**Complete if Known**	
				Application Number	**10/678,767**
				Filing Date	**October 3, 2003**
				First Named Inventor	**Srinivas G. Rao**
				Group Art Unit	
				Examiner Name	
Sheet	2	of	15	**Attorney Docket Number**	**CYPR 105/108**

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	US Patent Document Number	Kind Code[2] (if known)	Name of Patentee or Applicant of Cited Document	Date of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
CA		4,346,709		Schmitt	08-31-1982	
CA		4,353,887		Hess, et al.	10-12-1982	
CA		4,367,741		Michaels	01-11-1983	
CA		4,415,547		Yu, et al.	11-15-1983	
CA		4,428,925		Keith	01-31-1984	
CA		4,428,926		Keith	01-31-1984	
CA		4,432,965		Keith, et al.	02-21-1984	
CA		4,455,144		Michaels	06-19-1984	
CA		4,478,836		Mouzin, et al.	10-23-1984	
CA		4,482,533		Keith	11-13-1984	
CA		4,503,031		Glassman	03-05-1985	
CA		4,505,890		Jain, et al.	03-19-1985	
CA		4,508,702		Hsiao	04-02-1985	
CA		4,520,009		Dunn	05-28-1985	
CA		4,524,060		Mughal, et al.	06-18-1985	
CA		4,540,566		Davis, et al.	09-10-1985	
CA		4,556,678		Hsiao	12-03-1985	
CA		4,557,925		Lindahl, et al.	21-10-1985	
CA		4,571,333		Hsiao, et al.	02-18-1986	
CA		4,587,118		Hsiao	05-06-1986	
CA		4,610,870		Jain, et al.	09-09-1986	
CA		4,629,619		Lindahl, et al.	12-16-1986	
CA		4,629,620		Lindahl, et al.	12-16-1986	
CA		4,634,587		Hsiao	01-06-1987	
CA		4,649,043		Urquhart, et al.	03-10-1987	

Examine Signature	Carlos	Date Considered	1/26/07

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to application.

[1] Unique citation designation number [2] See attached Kinds of U.S. Patent Documents. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant to place a check mark here if English language Translation is attached.

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SENT TO: Assistant Commission for Patent, Washington, DC 20231.

Please type a plus sign (+) inside this box → [+]

PTO/SB/08A (10-96)
Approved for use through 10/31/99. OMB 0651-0031
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number

Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Complete if Known	
Application Number	**10/678,767**
Filing Date	**October 3, 2003**
First Named Inventor	**Srinivas G. Rao**
Group Art Unit	
Examiner Name	
Attorney Docket Number	**CYPR 105/108**

Sheet 3 of 15

U.S. PATENT DOCUMENTS						
Examiner Initials*	Cite No.[1]	US Patent Document		Name of Patentee or Applicant of Cited Document	Date of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number	Kind Code[2] (if known)			
CA		4,666,705		DeCrosta, et al.	05-19-1987	
CA		4,690,824		Powell, et al.	09-01-1987	
CA		4,692,337		Ukigaya	09-08-1987	
CA		4,695,467		Uemura, et al.	09-22-1987	
CA		4,695,591		Hanna, et al.	09-22-1987	
CA		4,708,834		Cohen, et al.	11-24-1987	
CA		4,710,384		Rotman	12-01-1987	
CA		4,734,285		Alderman	03-29-1988	
CA		4,740,198		Theeuwes	04-26-1988	
CA		4,756,911		Drost, et al.	07-12-1988	
CA		4,775,535		Lowey	10-04-1988	
CA		4,781,919		Liebowitz	11-01-1988	
CA		4,784,858		Ventouras	11-15-1988	
CA		4,795,327		Gaylord, et al.	01-03-1989	
CA		4,795,642		Cohen, et al.	01-03-1989	
CA		4,795,645		Friedman, et al.	01-03-1989	
CA		4,798,725		Patel	01-17-1989	
CA		4,800,083		Hom, et al.	01-24-1989	
CA		4,803,076		Ranade	02-07-1989	
CA		4,803,079		Hsiao, et al.	02-07-1989	
CA		4,806,359		Radebaugh, et al.	02-21-1989	
CA		4,816,262		McMullen	03-28-1989	
CA		4,820,522		Radebaugh, et al.	04-11-1989	
CA		4,822,619		Eichel, et al.	04-18-1989	
CA		4,824,678		Lindahl, et al.	04-25-1989	

Examine Signature	Carla	Date Considered	1/26/07

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to application.

[1] Unique citation designation number [2] See attached Kinds of U.S. Patent Documents. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant to place a check mark here if English language Translation is attached.

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SENT TO: Assistant Commission for Patent, Washington, DC 20231.

Please type a plus sign (+) inside this box → +

PTO/SB/08A (10-96
Approved for use through 10/31/99. OMB 0651-0031
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number

Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Complete if Known	
Application Number	**10/678,767**
Filing Date	**October 3, 2003**
First Named Inventor	**Srinivas G. Rao**
Group Art Unit	
Examiner Name	
Attorney Docket Number	**CYPR 105/108**

Sheet 4 of 15

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	US Patent Document Number	Kind Code[2] (if known)	Name of Patentee or Applicant of Cited Document	Date of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
CA		4,832,957		Dempski, et al.	05-23-1989	
CA		4,837,032		Ortega	06-06-1989	
CA		4,842,866		Horder, et al.	06-27-1989	
CA		4,849,229		Gaylord, et al.	07-18-1989	
CA		4,861,590		Grodberg	08-29-1989	
CA		4,863,743		Hsiao, et al.	09-05-1989	
CA		4,871,548		Edgren, et al.	10-03-1989	
CA		4,882,167		Jang	11-21-1989	
CA		4,892,742		Shah	01-09-1990	
CA		4,900,755		Dempski, et al.	02-13-1990	
CA		4,919,938		Lovegrove, et al.	04-24-1990	
CA		4,925,676		Ghebre-Sellassie	05-15-1990	
CA		4,933,185		Wheatley, et al.	06-12-1990	
CA		4,946,686		McClelland, et al.	08-07-1990	
CA		4,956,388		Robertson, et al.	09-11-1990	
CA		4,966,768		Michelucci, et al.	10-30-1990	
CA		4,968,509		Radebaugh, et al.	11-06-1990	
CA		4,983,398		Gaylord, et al.	01-08-1991	
CA		4,983,400		Dempski, et al.	01-08-1991	
CA		4,983,401		Eichel, et al.	01-08-1991	
CA		4,996,060		Eckenhoff, et al.	02-26-1991	
CA		5,002,774		Agrawal, et al.	03-26-1991	
CA		5,004,613		Radebaugh, et al.	04-02-1991	
CA		5,007,790		Shell		
CA		5,009,895		Lui		

Examine Signature		Date Considered	1/26/07

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to application.

[1] Unique citation designation number [2] See attached Kinds of U.S. Patent Documents. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant to place a check mark here if English language Translation is attached.

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SENT TO: Assistant Commission for Patent, Washington, DC 20231.

Please type a plus sign (+) inside this box → +

PTO/SB/08A (10-96)
Approved for use through 10/31/99. OMB 0651-0031
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number

Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 5 of 15

Complete if Known	
Application Number	10/678,767
Filing Date	October 3, 2003
First Named Inventor	Srinivas G. Rao
Group Art Unit	
Examiner Name	
Attorney Docket Number	CYPR 105/108

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.¹	US Patent Document Number	Kind Code² (if known)	Name of Patentee or Applicant of Cited Document	Date of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
CH		5,015,479		Mulligan, et al.	05-14-1991	
CH		5,019,398		Daste	05-28-1991	
CH		5,051,261		McGinity, et al.	09-24-1991	
CH		5,055,306		Barry, et al.	10-08-1991	
CH		5,057,318		Magruder, et al.	10-15-1991	
CH		5,073,380		Babu, et al.	12-17-1991	
CH		5,075,114		Roche	12-24-1991	
CH		5,085,865		Nayak	02-04-1992	
CH		5,091,189		Heafield, et al.	02-25-1992	
CH		5,112,614		Magruder, et al.	05-12-1992	
CH		5,126,145		Evenstad, et al.	06-30-1992	
CH		5,137,727		Eckenhoff	08-11-1992	
CH		5,162,117		Stupak	11-10-1992	
CH		5,164,193		Okada, et al.	11-17-1992	
CH		5,169,642		Brinker, et al.	11-08-1992	
CH		5,186,930		Kogan, et al.	02-16-1993	
CH		5,200,193		Radebaugh, et al.	04-06-1993	
CH		5,204,121		Bücheler, et al.	04-20-1993	
CH		5,219,572		Sivaramakrishnan	06-15-1993	
CH		5,230,901		Einig, et al.	06-27-1993	
CH		5,234,692		Magruder, et al.	08-10-1993	
CH		5,234,693		Magruder, et al.	08-10-1993	
CH		5,238,687		Magruder, et al.	08-24-1993	
CH		5,268,182		Brinker, et al.	12-07-1993	
CH		5,277,912		Lowe, et al.	01-11-1994	

Examine Signature		Date Considered	1/26/07

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to application.

¹ Unique citation designation number ² See attached Kinds of U.S. Patent Documents. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. ⁶ Applicant to place a check mark here if English language Translation is attached.

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SENT TO: Assistant Commission for Patent, Washington, DC 20231.

Please type a plus sign (+) inside this box → ☐

PTO/SB/08A (10-96
Approved for use through 10/31/99. OMB 0651-0031
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number

Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Complete If Known	
Application Number	**10/678,767**
Filing Date	**October 3, 2003**
First Named Inventor	**Srinivas G. Rao**
Group Art Unit	
Examiner Name	
Attorney Docket Number	**CYPR 105/108**

Sheet 6 of 15

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	US Patent Document Number	Kind Code[2] (if known)	Name of Patentee or Applicant of Cited Document	Date of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
CH		5,278,201		Dunn, et al.	01-11-1994	
CH		5,278,202		Dunn, et al.	01-11-1994	
CH		5,283,065		Doyon, et al.	02-01-1994	
CH		5,292,533		McMahon, et al.	03-08-1994	
CH		5,292,534		Valentine, et al.	03-08-1994	
CH		5,320,616		Magruder, et al.	06-14-1994	
CH		5,324,519		Dunn, et al.	06-28-1994	
CH		5,328,697		Raman, et al.	07-12-1994	
CH		5,334,392		Cuine, et al.	08-02-1994	
CH		5,334,393		Bougaret, et al.	08-02-1994	
CH		5,340,849		Dunn, et al.	08-23-1994	
CH		5,356,635		Raman, et al.	10-18-1994	
CH		5,358,723		Ghebre-Sellassie	10-25-1994	
CH		5,362,424		Lee, et al.	11-08-1994	
CH		5,366,738		Rork, et al.	11-22-1994	
CH		5,368,859		Dunn, et al.	11-29-1994	
CH		5,368,862		Colegrove	11-29-1994	
CH		5,393,765		Infeld, et al.	02-28-1995	
CH		5,397,574		Chen	03-14-1995	
CH		5,407,686		Patel, et al.	04-18-1995	
CH		5,413,572		Wong, et al.	05-09-1995	
CH		5,419,918		Lundberg	05-30-1995	
CH		5,424,289		Yang, et al.	06-13-1995	
CH		5,427,798		Ludwig, et al.	06-27-1995	
CH		5,427,799		Valentine, et al.	06-27-1995	

Examine Signature		Date Considered	1/26/07

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to application.

[1] Unique citation designation number [2] See attached Kinds of U.S. Patent Documents. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant to place a check mark here if English language Translation is attached.

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SENT TO: Assistant Commission for Patent, Washington, DC 20231.

Please type a plus sign (+) inside this box → ☐+

PTO/SB/08A (10-96)
Approved for use through 10/31/99. OMB 0651-0031
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number

Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 7 of 15

Complete if Known

Application Number	10/678,767
Filing Date	October 3, 2003
First Named Inventor	Srinivas G. Rao
Group Art Unit	
Examiner Name	
Attorney Docket Number	CYPR 105/108

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	US Patent Document Number	Kind Code (if known)	Name of Patentee or Applicant of Cited Document	Date of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
CH		5,433,951		Serajuddin, et al.	08-18-1995	
CH		5,455,046		Baichwal	10-03-1995	
CH		5,462,747		Radebaugh, et al.	10-31-1995	
CH		5,466,460		McMahon, et al.	11-14-1995	
CH		5,484,607		Horacek	01-16-1996	
CH		5,487,897		Polson, et al.	01-30-1996	
CH		5,492,700		Ghebre-Sellassie	02-20-1996	
CH		5,498,422		Nakamichi, et al.	03-12-1996	
CH		5,500,227		Oshlack, et al.	03-19-1996	
CH		5,505,962		Sparks	04-09-1996	
CH		5,508,041		Lee, et al.	04-16-1996	
CH		5,512,293		Landrau, et al.	04-30-1996	
CH		5,512,297		Baichwal	04-30-1996	
CH		5,540,912		Roorda, et al.	07-30-1996	
CH		5,543,155		Fekete, et al.	08-06-1996	
CH		5,554,387		Baichwal	09-10-1996	
CH		5,558,879		Chen, et al.	09-24-1996	
CH		5,562,915		Lowe, et al.	10-08-1996	
CH		5,576,021		Andoh, et al.	09-19-1996	
CH		5,578,321		Sherman	11-26-1996	
CH		5,582,837		Shell	12-10-1996	
CH		5,593,694		Hayashida, et al.	01-14-1997	
CH		5,599,552		Dunn, et al.	02-04-1997	
CH		5,601,842		Bartholomaeus	02-11-1997	
CH		5,603,956		Mateescu, et al.	02-18-1997	

Examine Signature		Date Considered	1/26/07

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to application.

[1] Unique citation designation number [2] See attached Kinds of U.S. Patent Documents. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant to place a check mark here if English language Translation is attached.

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SENT TO: Assistant Commission for Patent, Washington, DC 20231.

Please type a plus sign (+) inside this box → +

PTO/SB/08A (10-96
Approved for use through 10/31/99. OMB 0651-0031
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number

Substitute for form 1449A/PTO		Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (use as many sheets as necessary)		Application Number	10/678,767
		Filing Date	October 3, 2003
		First Named Inventor	Srinivas G. Rao
		Group Art Unit	
		Examiner Name	
Sheet 8	of 15	Attorney Docket Number	CYPR 105/108

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	US Patent Document Number	Kind Code[2] (if known)	Name of Patentee or Applicant of Cited Document	Date of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
CA		5,614,218		Olsson, et al.	03-25-1997	
CA		5,621,142		Mochizuki, et al.	04-15-1997	
CA		5,624,683		Andoh, et al.	04-29-1997	
CA		5,626,874		Conte, et al.	05-06-1997	
CA		5,630,808		Magruder, et al.	05-20-1997	
CA		5,643,602		Ulmius	07-01-1997	
CA		5,645,858		Kotwal, et al.	07-08-1997	
CA		5,650,170		Wright, et al.	07-22-1997	
CA		5,654,005		Chen, et al.	08-05-1997	
CA		5,656,291		Olsson, et al.	08-12-1997	
CA		5,660,837		Lundquist	08-26-1997	
CA		5,667,801		Baichwal	09-16-1997	
CA		5,681,582		Gilis, et al.	10-28-1997	
CA		5,681,583		Conte, et al.	10-28-1997	
CA		5,688,530		Bodmer, et al.	11-18-1997	
CA		5,690,960		Bengtsson, et al.	11-25-1997	
CA		5,702,716		Dunn, et al.	12-30-1997	
CA		5,705,190		Broad, et al.	01-06-1998	
CA		5,707,655		Kanikanti, et al.	01-13-1998	
CA		5,733,950		Dunn, et al.	03-31-1998	
CA		5,736,152		Dunn	04-07-1998	
CA		5,736,159		Chen, et al.	04-07-1998	
CA		5,739,176		Dunn, et al.	04-14-1998	
CA		5,744,153		Yewey, et al.	04-28-1998	
CA		5,759,563		Yewey, et al.	06-02-1998	

Examiner Signature		Date Considered	1/26/07

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to application.

[1] Unique citation designation number [2] See attached Kinds of U.S. Patent Documents. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant to place a check mark here if English language Translation is attached.

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SENT TO: Assistant Commission for Patent, Washington, DC 20231.

Please type a plus sign (+) inside this box → [+]

PTO/SB/08A (10-96)
Approved for use through 10/31/99. OMB 0651-0031
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number

Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 9 of 15

Complete if Known	
Application Number	10/678,767
Filing Date	October 3, 2003
First Named Inventor	Srinivas G. Rao
Group Art Unit	
Examiner Name	
Attorney Docket Number	CYPR 105/108

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	US Patent Document Number	Kind Code[2] (if known)	Name of Patentee or Applicant of Cited Document	Date of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
CK		5,776,489		Preston, et al.	07-07-1998	
CK		5,780,044		Yewey, et al.	07-14-1998	
CK		5,783,212		Fassihi, et al.	07-21-1998	
CK		5,846,563		Baichwal	12-08-1998	
CK		5,849,330		Marvola, et al.	12-15-1998	
CK		5,861,166		Eckenhoff	01-19-1999	
CK		5,869,100		Horacek	02-09-1999	
CK		5,874,107		Fischer, et al.	02-23-1999	
CK		5,879,707		Cartilier, et al.	03-09-1999	
CK		5,882,682		Rork, et al.	03-16-1999	
CK		5,885,615		Chouinard, et al.	03-23-1999	
CK		5,888,533		Dunn	03-30-1999	
CK		5,900,425		Kanikanti, et al.	05-04-1999	
CK		5,945,115		Dunn, et al.	08-31-1999	
CK		5,945,125		Kim	08-31-1999	
CK		5,980,942		Katzhendler, et al.	11-09-1999	
CK		5,990,194		Dunn, et al.	11-23-1999	
CK		6,010,718		Al-Razzak, et al.	01-04-2000	
CK		6,024,982		Oshlack, et al.	02-15-2000	
CK		6,027,748		Conte, et al.	02-22-2000	
CK		6,030,641		Yamashita, et al.	02-29-2000	
CK		6,030,642		Horacek	02-29-2000	
CK		6,033,685		Qiu, et al.	03-07-2000	
CK		6,033,686		Seth	03-07-2000	
CK		6,046,177		Stella, et al.	04-04-2000	

Examine Signature		Date Considered	1/26/07

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to application.

[1] Unique citation designation number [2] See attached Kinds of U.S. Patent Documents. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant to place a check mark here if English language Translation is attached.

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SENT TO: Assistant Commission for Patent, Washington, DC 20231.

Please type a plus sign (+) inside this box → ☐

PTO/SB/08A (10-96
Approved for use through 10/31/99. OMB 0651-0031
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number

Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Complete if Known	
Application Number	**10/678,767**
Filing Date	**October 3, 2003**
First Named Inventor	**Srinivas G. Rao**
Group Art Unit	
Examiner Name	
Attorney Docket Number	**CYPR 105/108**

Sheet 10 of 15

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	US Patent Document		Name of Patentee or Applicant of Cited Document	Date of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number	Kind Code[2] (if known)			
CH		6,056,977		Bhagwat, et al.	05-02-2000	
CH		6,074,669		Nagaprasad, et al.	06-13-2000	
CH		6,077,538		Merrill, et al.	06-20-2000	
CH		6,083,533		Cremer	07-04-2000	
CH		6,090,411		Pillay, et al.	07-18-2000	
CH		6,093,387		Birbara, et al.	07-25-2000	
CH		6,099,859		Cheng, et al.	08-08-2000	
CH		6,099,862		Chen, et al.	08-08-2000	
CH		6,106,863		Ukigaya, et al.	08-22-2000	
CH		6,113,938		Chen, et al.	09-05-2000	
CH		6,120,789		Dunn	09-19-2000	
CH		6,126,967		Clemente, et al.	10-03-2000	
CH		6,136,343		Baichwal	10-24-2000	
CH		6,143,314		Chandrashekar, et al.	11-07-2000	
CH		6,143,353		Oshlack, et al.	11-07-2000	
CH		6,149,940		Maggi, et al.	11-21-2000	
CH		6,150,396		Iyengar, et al.	11-21-2000	
CH		6,150,410		Engh, et al.	11-21-2000	
CH		6,156,343		Morita, et al.	12-05-2000	
CH		6,162,463		Lippa	12-19-2000	
CH		6,162,466		Licht, et al.	12-19-2000	
CH		6,174,547		Dong, et al.	01-16-2001	
CH		6,180,129		Magruder, et al.	01-30-2001	
CH		6,197,339		Ju	03-06-2001	
CH		6,197,344		Chang, et al.	03-06-2001	

Examine Signature		Date Considered	1/26/07

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to application.

[1] Unique citation designation number [2] See attached Kinds of U.S. Patent Documents. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant to place a check mark here if English language Translation is attached.

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SENT TO: Assistant Commission for Patent, Washington, DC 20231.

Please type a plus sign (+) inside this box → ☐ +

PTO/SB/08A (10-96
Approved for use through 10/31/99. OMB 0651-0031
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number

Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Complete If Known	
Application Number	**10/678,767**
Filing Date	**October 3, 2003**
First Named Inventor	**Srinivas G. Rao**
Group Art Unit	
Examiner Name	
Attorney Docket Number	**CYPR 105/108**

Sheet 11 of 15

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	US Patent Document Number	Kind Code[2] (if known)	Name of Patentee or Applicant of Cited Document	Date of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
CK		6,210,714		Oshlack, et al.	04-03-2001	
CK		6,221,395		Maggi, et al.	04-24-2001	
CK		6,245,357		Edgren, et al.	06-12-2001	
CK		6,251,432		Mazer, et al.	06-26-2001	
CK		6,254,891		Anaebonam, et al.	07-03-2001	
CK		6,261,583		Dunn, et al.	07-17-2001	
CK		6,261,601		Talwar, et al.	07-17-2001	
CK		6,270,799		Siefert, et al.	08-07-2001	
CK		6,274,171		Sherman, et al.	08-14-2001	
CK		6,284,275		Chen, et al.	09-04-2001	
CK		6,303,144		Omura	10-16-2001	
CK		6,316,031		Oshlack, et al.	11-31-2001	
CK		6,337,091		Kim, et al.	01-08-2002	
CK		6,342,249		Wong, et al.	01-29-2002	
CK		6,365,196		Venkatesh, et al.	04-02-2002	
CK		6,368,626		Bhatt, et al.	04-09-2002	
CK		6,372,252		Blume, et al.	04-16-2002	
CK		6,375,978		Kleiner, et al.	04-23-2002	
CK		6,387,404		Oshlack, et al.	05-14-2002	
CK		6,395,292		Peery, et al.	05-28-2002	
CK		6,403,120		Sherman, et al.	06-11-2002	
CK		6,416,786		Mulye, et al.	07-09-2002	
CK		6,419,952		Wong, et al.	07-16-2002	
CK		6,419,953		Qiu, et al.	07-16-2003	
CK		6,419,958		Sherman, et al.	07-16-2002	

Examine Signature		Date Considered	1/26/07

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to application.

[1] Unique citation designation number [2] See attached Kinds of U.S. Patent Documents. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant to place a check mark here if English language Translation is attached.

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SENT TO: Assistant Commission for Patent, Washington, DC 20231.

Please type a plus sign (+) inside this box → ☐+

PTO/SB/08A (10-96
Approved for use through 10/31/99. OMB 0651-0031
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number

Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 12 of 15

Complete If Known	
Application Number	10/678,767
Filing Date	October 3, 2003
First Named Inventor	Srinivas G. Rao
Group Art Unit	
Examiner Name	
Attorney Docket Number	CYPR 105/108

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	US Patent Document Number	Kind Code[2] (if known)	Name of Patentee or Applicant of Cited Document	Date of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
CK		6,426,091		Okumura, et al.	07-30-2003	
CK		6,437,000		Mulye	08-20-2002	
CH		6,441,038		Loder, et al.	08-27-2002	
CH		6,461,631		Dunn, et al.	10-08-2002	
CH		6,475,521		Timmins, et al.	11-05-2002	
CH		6,491,950		Gutierrez-Rocca	12-10-2002	
CH		6,492,488		Adams, et al.	12-10-2002	
CH		6,495,162		Cheng, et al.	12-17-2002	
CH		6,500,454		Percel, et al.	12-31-2002	
CH		RE 35,601		Eckenhoff	09-02-1997	
CH		RE 37,950		Dunn, et al.	12-31-2002	

Examine Signature		Date Considered	1/26/07

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to application.

[1] Unique citation designation number [2] See attached Kinds of U.S. Patent Documents. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant to place a check mark here if English language Translation is attached.

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SENT TO: Assistant Commission for Patent, Washington, DC 20231.

Please type a plus sign (+) inside this box → ☐

PTO/SB/08A (10-96)
Approved for use through 10/31/99. OMB 0651-0031
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number

Substitute for form 1449A/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (use as many sheets as necessary)				**Complete If Known**	
				Application Number	**10/678,767**
				Filing Date	**October 3, 2003**
				First Named Inventor	**Srinivas G. Rao**
				Group Art Unit	
				Examiner Name	
Sheet	13	of	15	**Attorney Docket Number**	**CYPR 105/108**

OTHER ART -- NON PATENT LITERATURE DOCUMENTS			
Examiner's Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published	T[2]
CA		AL-CHAER, et al., "A new model of chronic visceral hypersensitivity in adult rats induced by colon irritation during postnatal development," *Gastroenterology* 119: 1276-1285 (2000).	
CA		BEL & ARTIGAS, "Modulation of the extracellular 5-hydroxytryptamine brain concentrations by the serotonin and noradrenaline reuptake inhibitor, milnacipran. Microdialysis studies in rats," *Neuropsychopharmacology* 21(6): 745-754 (1999).	
CA		CACCIA, "Metabolism of the newer antidepressants: an overview of the pharmacological and pharmacokinetic implications," *Clin. Pharmacokinet.* 34(4): 281-302 (1998).	
CA		CHOU & TALALAY, "Quantitative analysis of dose-effect relationships: the combined effects of multiple drugs or enzyme inhibitors," *Adv. Enzyme Regul.* 22: 27-55 (1984).	
CA		DEPREZ, et al., "Which bioequivalence study for a racemic drug? Application to milnacipran," *Eur. J. Drug Metab. Pharmacokinet.* 23(2): 166-171 (1998).	
CA		DOYLE & HU, "A new enantioselective synthesis of milnacipran and an analogue by catalytic asymmetric cyclopropanation," *Adv. Synth. Catal.* 343(3): 299-302 (2001).	
CA		EISEN, "Venflaxine therapy for vulvodynia," *The Pain Clinic* 8(4): 365-367 (1995).	
CA		GIAMBERARDINO, "Recent and forgotten aspects of visceral pain," *Eur. J. Pain* 3: 77-92 (1999).	
CA		HUFFMAN, et al., "Lithium alkoxides of cinchona alkaloids as chiral controllers for enantioselective acetylide addition to cyclic N-acyl ketimines," *J. Org. Chem.* 60: 1590-1594 (1995).	
CA		MOCHIZUKI, et al., "Neurochemical and behavioural characterization of milnacipran, a serotonin and noradrenaline reuptake inhibitor in rats," *Psychopharmacology* 162: 323-332 (2002).	

Examiner's Signature	Carlos	Date Considered	1/26/07

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] Unique citation designation number [2] See attached Kinds of U.S. Patent Documents. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant to place a check mark here if English language Translation is attached.

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you require to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

Notice of References Cited	Application/Control No. 10/678,767	Applicant(s)/Patent Under Reexamination RAO ET AL.	
	Examiner Carlic K. Huynh	Art Unit 1617	Page 1 of 2

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-6,602,911	08-2003	Kranzler et al.	514/624
*	B	US-6,635,675	10-2003	Kranzler et al.	514/620
*	C	US-6,992,110	01-2006	Kranzler et al.	514/620
*	D	US-2003/0203055	10-2003	Rao et al.	514/649
*	E	US-2003/0232805	12-2003	Kranzler et al.	514/217
*	F	US-2004/0014739	01-2004	Koppel, Gary A.	514/210.09
*	G	US-2004/0019116	01-2004	Kranzler et al.	514/620
*	H	US-2004/0034101	02-2004	Rao et al.	514/619
*	I	US-2004/0132826	07-2004	Hirsh et al.	514/620
*	J	US-2005/0032782	02-2005	Rao et al.	514/220
*	K	US-2005/0096395	05-2005	Rao et al.	514/649
*	L	US-2006/0024366	02-2006	Hirsh et al.	424/468
*	M	US-2006/0039866	02-2006	Rao et al.	424/045

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Kranzler, J.D., Gendreau, J.F., and Rao, S.G. The Psychopharmacology of Fibromyalgia: A Drug Development Perspective. 2002. Vol. 36, No. 1. pp. 165-213.
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Notice of References Cited	Application/Control No. 10/678,767	Applicant(s)/Patent Under Reexamination RAO ET AL.
	Examiner Carlic K. Huynh	Art Unit 1617
		Page 2 of 2

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-2006/0039867	02-2006	Rao et al.	424/045
*	B	US-2007/0021352	01-2007	Anderson et al.	514/018
*	C	US-11/535,237	09-2006	Rao et al.	514/303
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Please type a plus sign (+) inside this box → ☐ +

PTO/SB/08A (10-96
Approved for use through 10/31/99. OMB 0651-0031
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number

Substitute for form 1449A/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (use as many sheets as necessary)				**Complete If Known**	
				Application Number	**10/678,767**
				Filing Date	**October 3, 2003**
				First Named Inventor	**Srinivas G. Rao**
				Group Art Unit	
				Examiner Name	
Sheet	14	of	15	**Attorney Docket Number**	**CYPR 105/108**

OTHER ART – NON PATENT LITERATURE DOCUMENTS

Examiner's Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published	T[2]
CH		MORET & BRILEY, "Effects of milnacipran and pindolol on extracellular noradrenaline and serotonin levels in guinea pig hypothalamus," *J. Neurochem.* 69(2): 815-822 (1997).	
CH		MORET, et al., "Biochemical profile of midalcipran (F 2207), 1-phenyl-1-diethyl-aminocarbonyl-2-aminomethyl-cyclopropane (Z) hydrochloride, a potential fourth generation antidepressant drug," *Neuropharmacology* 24(12): 1211-1219 (1985).	
CH		MUGNAINI, et al., "Receptor binding characteristics of the novel NMDA receptor glycine site antagonist [3H]GV150526A in rat cerebral cortical membranes," *Eur. J. Pharmacol.* 391: 233-241 (2000).	
CH		NALIBOFF, et al., "Evidence for two distinct perceptual alterations in irritable bowel syndrome," *Gut* 41: 505-512 (1997).	
CH		PALMIER, et al., "Monoamine uptake inhibition by plasma from healthy volunteers after single oral doses of the antidepressant milnacipran," *Eur. J. Clin. Pharmacol.* 37(3): 235-238 (1989).	
CH		SANCHEZ & HYTTEL, "Comparison of the effects of antidepressants and their metabolites on reuptake of biogenic amines and on receptor binding," *Cell. Mol. Neurobiol.* 19(4): 467-489 (1999).	
CH		SCHOEMAKER, et al., "Binding of [3H]ifenprodil, a novel NMDA antagonist, to a polyamine-sensitive site in the rat cerebral cortex," *Eur. J. Pharmacol.* 176: 249-250 (1990).	
CH		SHUTO, et al., "(+/-)-(Z)-2-(aminomethyl)-1-phenylcyclopropanecarboxamide derivatives as a new prototype of NMDA receptor antagonists," *J. Med. Chem.* 38: 2964-2968 (1995).	
CH		SHUTO, et al., "(1S,2R)-1-Phenyl-2-[(S)-1-aminopropyl]-N,N-diethylcyclopropanecarboxamide (PPDC), a new class of NMDA-receptor antagonist: molecular design by a novel conformational restriction strategy," *Jpn. J. Pharmacol.* 85: 207-213 (2001).	
CH		SHUTO, et al., "Synthesis and biological activity of conformationally restricted analogs of milnacipran: (1S,2R)-1-phenyl-2-[(S)-1-aminopropyl]-N,N-diethylcyclopropanecarboxami de, an efficient noncompetitive N-methyl-D-aspartic acid receptor antagonist," *J. Med. Chem.* 39: 4844-4852 (1996).	

Examiner's Signature	Carlie Hugh	Date Considered	1/26/07

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] Unique citation designation number [2] See attached Kinds of U.S. Patent Documents. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant to place a check mark here if English language Translation is attached.

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you require to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

Please type a plus sign (+) inside this box → ☐ +

PTO/SB/08A (10-96
Approved for use through 10/31/99. OMB 0651-0031
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number

Substitute for form 1449A/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** (use as many sheets as necessary)				**Complete if Known**	
				Application Number	**10/678,767**
				Filing Date	**October 3, 2003**
				First Named Inventor	**Srinivas G. Rao**
				Group Art Unit	
				Examiner Name	
Sheet	15	of	15	**Attorney Docket Number**	**CYPR 105/108**

OTHER ART -- NON PATENT LITERATURE DOCUMENTS			
Examiner's Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published	T[2]
CH		SHUTO, et al., "Synthesis and biological activity of conformationally restricted analogues of milnacipran: (1S, 2R)-1-phenyl-2-[(R)-1-amino-2-propynyl]-N,N- diethylcyclopropanecarboxamide is a novel class of NMDA receptor channel blocker," *J. Med. Chem.* 41: 3507-3514 (1998).	
CH		SHUTO, et al., "Synthesis of (+)- and (-)-milnaciprans and their conformationally restricted analogs," *Tetrahedron Lett.* 37(5): 641-644 (1996).	
CH		TALLEY & SPILLER, "Irritable bowel syndrome: a little understood organic bowel disease?" *Lancet* 360: 555-564 (2002).	
CH		TUCKER, et al, "Synthesis of a series of 4-(arylethynyl)-6-chloro-4-cyclopropyl-3,4-dihydroquinazolin-2(1H)-ones as novel non-nucleoside HIV-1 reverse transcriptase inhibitors," *J. Med. Chem.* 37: 2437-2444 (1994).	
CH		TURCOTTE, et al., "Assessment of the serotonin and norepinephrine reuptake blocking properties of duloxetine in healthy subjects," *Neuropsychopharmacology* 24(5): 511-521 (2001).	
CH		VIAZZO, et al., "Microbioligical transformations 34: enantioselective hydrolysis of a key-lactone involved in the synthesis of the antidepressant milnacipran," *Tetrahedron Lett.* 37(26): 4519-4522 (1996).	
CH		YOSHIMURA, et al., "The involvement of the tetrodotoxin-resistant sodium channel $Na_v1.8$ (PN3/SNS) in a rat model of visceral pain," *J. Neurosci.* 21(21): 8690-8696 (2001).	
CH		ZUBAY, Biochemistry, 2nd ed., Macmillan: New York, pp. 259-283 (1988).	

Examiner's Signature	Carlos	Date Considered	1/26/07

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] Unique citation designation number [2] See attached Kinds of U.S. Patent Documents. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant to place a check mark here if English language Translation is attached.

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you require to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

Please type a plus sign (+) inside this box → ☐

PTO/SB/08A (10-96
Approved for use through 10/31/99. OMB 0651-0031
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

OIPE
FEB 28 2007
IAP26
PATENT & TRADEMARK OFFICE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number

Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

OIPE
JUL 29 2004
JCS
PATENT & TRADEMARK OFFICE

Complete if Known	
Application Number	**10/678,767**
Filing Date	**October 3, 2003**
First Named Inventor	**Srinivas G. Rao**
Group Art Unit	**1617**
Examiner Name	
Attorney Docket Number	**CYPR 105/108**

Sheet of 1

OTHER ART – NON PATENT LITERATURE DOCUMENTS

Examiner's Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published	T[2]
CH		SPENCER, "Milnacipran – A review of its use in depression," *Drugs*, 56(3): 405-427 (1998)	

Examiner's Signature		Date Considered	1/26/07

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to application.

[1] Unique citation designation number [2] See attached Kinds of U.S. Patent Documents. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant to place a check mark here if English language Translation is attached.

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SENT TO: Assistant Commission for Patent, Washington, DC 20231.

OIPE
AUG 2 4 2005
PATENT & TRADEMARK

PTO/SB/08a/b (08-03)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449A/B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet	1	of	1

Complete If Known	
Application Number	10/678,767
Filing Date	October 3, 2003
First Named Inventor	Srinivas G. Rao
Art Unit	1617
Examiner Name	S. J. Sharareh
Attorney Docket Number	20269/1201781-US4

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
CA	AA**	US-2002/0086864-A1	07-04-2002	Wong et al.	
CA	AB**	US-6,451,788-B1	09-17-2002	Horrobin et al.	
CA	AC**	US-6,194,000-B1	02-27-2001	Smith et al.	
CA	AD**	US-2002/0147196-A1	10-10-2002	Quessy et al.	
CA	AE**	US-2002/0156067-A1	10-24-2002	Wong et al.	
CA	AF**	US-6,489,341-B1	12-03-2002	Jerussi	
CA	AG**	US-6,441,038-B1	08-27-2002	Loder et al.	
CA	AH**	US-2002/0035105-A1	03-21-2002	Caruso	
CA	AI**	US-5,945,416-A	08-31-1999	Shannon et al.	
CA	AJ**	US-5,352,683-A	10-04-1994	Mayer et al.	
CA	AK**	US-2002/0187958-A1	12-12-2002	Horrobin et al.	
CA	AL**	US-2002/0072543-A1	06-13-2002	Olesen et al.	
CA	AM**	US-2003/0013689-A1	01-16-2003	Helton et al.	
CA	AN**	US-2001/0036943-A1	11-01-2001	Coe et al.	

** Pursuant to the Notice issued by the United States Patent and Trademark Office dated July 11, 2003 waiving the requirements of 37 C.F.R. § 1.98(a)(2)(i), a copy/copies of the United States Patent on PTO/SB08 is/are not being submitted.

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
CA	CA	GOODNICK, Paul J., et al., "Bupropion Slow-Release Response in Depression: Diagnosis and Biochemistry", Biol. Psychiatry, 1998, Vol. 44, pp. 629-632.	
CA	CB	RAO, Srinivas G., et al., "Pharmacological therapies in fibromyalgia", Best Practice & Research Clinical Rheumatology, 2003, Vol. 17, No. 4, pp. 611-627.	
CA	CC	WANG, Richard I. H., et al., "The Oral Analgesic Efficacy of Bicifadine Hydrochloride in Postoperative Pain", J. Clin. Pharmacol., 1982, Vol. 22, pp. 160-164.	
CA	CD	PORTER, E. J. B., et al., "Single Dose Comparison of Bicifadine, Codeine and Placebo in Postoperative Pain", Current Therapeutic Research, August 1981, Vol. 30, No. 3, pp. 156-160.	
CA	CE	FISHBAIN, David, "Evidence-based data on pain relief with antidepressants", Ann. Med., 2000, Vol. 32, pp. 305-316.	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

Examiner Signature		Date Considered	1/26/07

Key Words: depression, drug development, fibromyalgia, neuroendocrine, neurokinin, neuropathic pain, norepinephrine, serotonin, stress

The Psychopharmacology of Fibromyalgia: A Drug Development Perspective

By Jay D. Kranzler, MD, PhD,
Judith F. Gendreau, MD, and Srinivas G. Rao, MD, PhD

Author Reprint

ABSTRACT ~ *The fibromyalgia syndrome (FMS) is the most frequent cause of chronic widespread pain. In this review, we summarize the state of the art on the syndrome and its pathophysiology, with an emphasis on identifying bases for the development of novel therapies. Toward this end, the anatomy and physiology of pain pathways are summarized, followed by a review of the altered biology of pain processing, neurotransmitter function, and neuroendocrine systems in FMS. The categories of drugs currently employed to treat the disorder are detailed, along with a critical review of the literature supporting such use. Throughout the article, FMS is compared with and related to both major depressive disorder and neuropathic pain, conditions that may share some common biological processes with FMS but for which new drug discovery efforts are significantly more active due to the more established nature of these diagnoses.* Psychopharmacology Bulletin. *2002;36(1):165–213*

Introduction

The fibromyalgia syndrome (FMS) is the most frequent cause of chronic, widespread pain and is estimated to affect 2% to 4% of the population.[1-3] FMS is second only to osteoarthritis (OA) as the most common diagnosis made in rheumatology practice and is diagnosed four times more frequently in women than in men.[4] It is considered one of the so-called "unexplained clinical conditions"[5] or "functional somatic syndromes . . . characterized more by symptoms, suffering, and disability than by consistent tissue abnormality."[6] The syndrome, as defined by the American College of Rheumatology's criteria established in 1990,[4] requires that pain be present for more than 3 months in all four quadrants of the body, as well as along the

---

Dr. Kranzler is chairman of the board and chief executive officer, Dr. Gendreau is director of medical affairs, and Dr. Rao is chief scientific officer, all at Cypress Bioscience, Inc. in San Diego, CA.

To whom correspondence should be addressed: Jay D. Kranzler, MD, PhD, Cypress Bioscience, Inc., 4350 Executive Drive, Suite 325, San Diego, CA 92121; Tel: (858) 452-2323; Fax: (858) 452-1222; E-mail: jkranzler@cypressbio.com

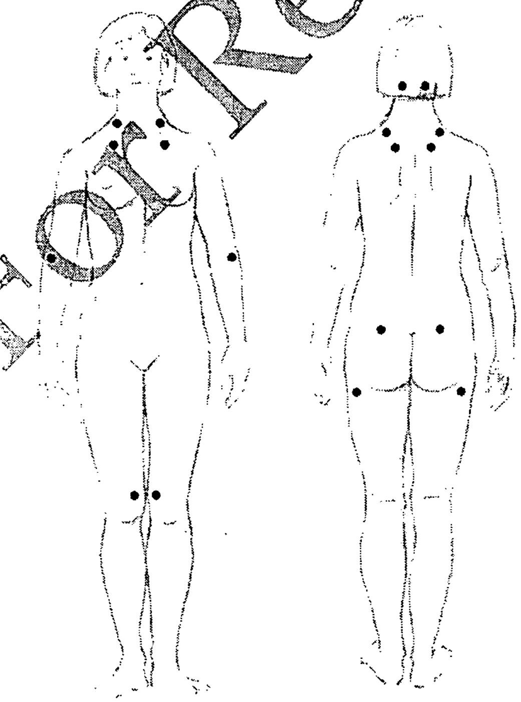
spine. In addition, pain must be elicited at 11 out of 18 "tender points" upon palpation (Figure 1). Although not required for diagnosis per se, other complaints, such as fatigue, nonrestorative sleep, and memory difficulties, have also been reported by the majority of patients (Table 1).[7] FMS can cause severe disability, comparable to that seen in other rheumatic diseases such as OA or rheumatoid arthritis (RA).[8,9]

There are many reasons why FMS remains a controversial diagnosis more than 10 years after the establishment of the diagnostic criteria. Some experts express concern for the individual patient and suggest that placing a label on these individuals promotes helplessness and disability.[10,11] Others focus on the legal and social consequences of identi-

FIGURE 1

Fibromyalgia Tender Points

Location of the 18 tender points used in the diagnosis of the fibromyalgia syndrome, per the American College of Rheumatology's 1990 criteria.[4]



Adapted from: Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum.* 1990;33:160-172.

Kranzler JD, Gendreau JF, Rao SG. *Psychopharmacology Bulletin.* Vol 36. No 1. 2002.

Not For Reprint

fying FMS as a disorder that can be caused by certain exposures (eg, motor vehicle accidents) and promote litigation.[12] Yet others question the validity of the criteria for diagnosis, especially the requirement for a certain number of tender points.[13,14]

Although there has been some suggestion that FMS may represent a form of somatization disorder, there is increasing evidence and acceptance that, notwithstanding its etiology, FMS is a medical problem reflecting a generalized heightened perception of sensory stimuli.[15-17] The abnormality is thought to occur within the central nervous system (CNS) rather than peripherally,[18] and the proposed pathophysiological defect is termed "central sensitization."[15-18] FMS patients typically suffer from both allodynia—perceiving pain even from a nonpainful stimulus such as light touch—and hyperalgesia—an augmentation of pain processing in which a painful stimulus is magnified and perceived with higher intensity than it would be by a normal subject.[19,20] In this regard, there are many parallels between the clinical presentation and the proposed underlying mechanisms of FMS and other forms of neuropathic pain such as diabetic neuropathy and trigeminal neuralgia.[21-23] As a result, FMS is treated today primarily within the medical model. It is diagnosed most often in the primary care setting, with almost half of FMS-related office visits to internal medicine and family practice providers.[24] Rheumatologists are the leading specialty group treating FMS patients; 16% of office visits made by FMS patients are to this group of physicians. The remainder of office visits are to a vari-

TABLE 1

Frequency of Symptoms in Patients With Fibromyalgia (at the Time of Diagnosis)

SYMPTOM	% OF PATIENTS AFFECTED
Muscular pain	100
Fatigue	96
Insomnia	86
Joint pains	72
Headaches	60
Restless legs	56
Paresthesias	52
Impaired memory	46
Leg cramps	42
Impaired concentration	41
Nervousness	32
Major depression	20

Adapted with permission. McCain GA. Fibromyalgia and myofascial pain. In: Wall PD, Melzack R, eds. *Textbook of Pain*. 3rd ed. Edinburgh, UK: Churchill Livingstone; 1994:475-493.

Kranzler JD, Gendreau JF, Rao SG. *Psychopharmacology Bulletin*. Vol 36. No 1. 2002.

ety of tertiary care providers, including pain centers, physical medicine specialists, and psychiatrists.

Despite the improved understanding that has developed over the past decade about the syndrome, much remains unknown. According to a longitudinal study by Wolfe et al[25] that reviewed the outcomes of patients followed serially at leading FMS referral centers in the United States, only a small percentage of the patients were found to have improved significantly by the end of 10 years of follow-up. Moreover, to this day, significant variability exists in the veracity of the diagnosis, treatment algorithms, and means to monitor outcomes. This lack of standardization further complicates the ability to gain knowledge and insight from collective experience.

The goals of this article are 2-fold and differ from several excellent reviews that have preceded it.[15,26-28] First, our summary of the existing literature is targeted to a psychiatric audience. Second, our perspective throughout the review is that of a group with an interest in developing novel pharmaceutical approaches to treat the syndrome. We will elaborate on each goal.

Psychosocial Aspects of Fibromyalgia Syndrome

To the best of our knowledge, this article represents the first comprehensive review of the biological aspects of FMS within the recent psychiatric literature, independent of the context of chronic fatigue syndrome (CFS) as a comparator. Our focus on areas of interest to the psychiatric community is meant to bridge a gap that we perceive between two constituencies—rheumatologists and psychiatrists—each of whom can contribute to further the state of the art of FMS treatment. Rheumatologists and other specialists and primary care providers who treat FMS patients day-to-day best understand the clinical syndrome and the differential diagnosis on presentation. However, cooperating and collaborating with the psychiatric community has the potential to improve clinical care, as well as to lead to a better understanding of the pathophysiology of FMS.

As described above, FMS is defined by pain, and, as such, pain is the central symptom that must be addressed by any effective therapy. However, it is clear that psychosocial elements play a role in symptom expression. Approximately 20% to 40% of individuals with FMS have an identifiable current mood disorder, such as depression or an anxiety disorder, at the time of diagnosis, with a lifetime incidence rate as high as 70%.[29-31] These data are among those used by Hudson and colleagues[31] to posit that there is a spectrum of conditions, including FMS, migraine headaches, irritable bowel syndrome, and affective disorders, which may share a common genetic predisposition and, perhaps, underlying pathogenic mechanisms. Cognitive behavioral therapy has been used successfully with some patients who have FMS, as well as with patients who have many of these other medical conditions.[32,33]

Some of the differences in the current and lifetime history of mood disorders, however, are likely due to healthcare-seeking behaviors, since lower lifetime incidences of affective disorders are noted typically in individuals with FMS who are identified in the general population.[34]

Psychopharmacology as a Link to Drug Development

Our second objective in this review is to present the existing data within a psychopharmacologic context, with the goal of identifying and developing new therapies by building on what is already known. Although FMS is clearly multifactorial in its etiology, variable in its natural history, and complex biologically, we view activities directed toward the discovery and development of novel drugs as feasible and necessary. FMS patients share certain neurochemical and neurohormonal changes with some psychiatric patient cohorts, and both groups respond to many psychotropic drugs in similar ways. In addition, most psychiatric diseases, like FMS, conform to the characteristics of "functional somatic syndromes" as defined previously. As a result, the nature of the challenges facing both basic and clinical scientists is similar and stems from trying to identify the proverbial "needle in the haystack"—a discrete primary CNS defect within the complex circuitry of neural pathways and feedback loops. In both cases, investigators are handicapped further by the lack of direct access to the living human brain and by the difficulty of sorting through cause and effect in a population presenting with multiple symptoms that is, obviously, subject to biological as well as psychosocial stressors, which may both contribute to pathophysiology. Despite these obstacles, enormous advances in our understanding of psychiatric disease have resulted from observation and analysis of patient responses to existing drugs, as well as from a willingness to use new agents as probes to test biological hypotheses. Through this process, new disorders have been defined (eg, social phobia), the definitions of existing disorders have been revised and/or segmented (eg, depression, obsessive-compulsive disorder), data have been gleaned to support or refute existing biological hypotheses, and new mechanisms have been identified. We believe this will be a productive and efficient approach to FMS as well.

Therefore, we have intentionally used depression and neuropathic pain instead of CFS as the comparators throughout this review; the existing scientific and clinical knowledge in these two areas related to

FMS (but not to each other) can serve as a useful springboard for formulating ideas for pharmaceutical development toward the treatment of FMS. Although there are certainly many similarities and a high degree of coincidence between FMS and CFS, the former, in which pain is the most prominent symptom, is probably more amenable to drug therapy than is CFS, which is characterized in its clinical presentation by primacy of fatigue.[35-37]

The body of this review will be divided into three parts. First, as FMS is a clinical demonstration of the existing links between pain sensation, the stress response, and mood, we briefly describe the neuroanatomy, pharmacology, and connectivity of the relevant pathways. Second, we review the neurochemical and neuroendocrinological differences that have been found in FMS patients and compare these observations with other conditions, where appropriate. Third, we summarize the literature on the effectiveness of drugs in treating FMS, and we try, where possible, to relate the empirical findings to both normal physiology and FMS pathophysiology. Throughout the discussion, we draw parallels between the features of FMS and two comparator disorders (depression and neuropathic pain) that have been studied more extensively. Finally, we attempt to summarize and present an integrated view of the syndrome along with ideas related to drug development.

Overview of Pain Processing Pathways

It has been recognized for some time that nociception is not a passive, unidirectional process[38]; rather, there is a complex interaction between ascending and descending pathways with the ability to alter dramatically the relationship between stimulus and response (see Figure 2).[39] Nociceptive input from the periphery is relayed via peripheral afferent fibers (PAF) to the dorsal horn of the spinal cord. After significant local processing, signals are sent to higher centers, and these impulses form the basis for pain perception. The two major descending pain-modulation systems employ the neurotransmitters serotonin (5-HT) and norepinephrine (NE), and originate from the rostral ventromedial medulla (RVM) and the dorsolateral pontine catecholamine cell groups (DLP), respectively. At the level of the spinal cord, the projections from the RVM appear to have both pro- and antinociceptive effects, whereas the pontine projections appear to be mainly antinociceptive. These two descending systems are interconnected tightly,[40] and their respective antinociceptive effects appear to be additive under some circumstances.[41]

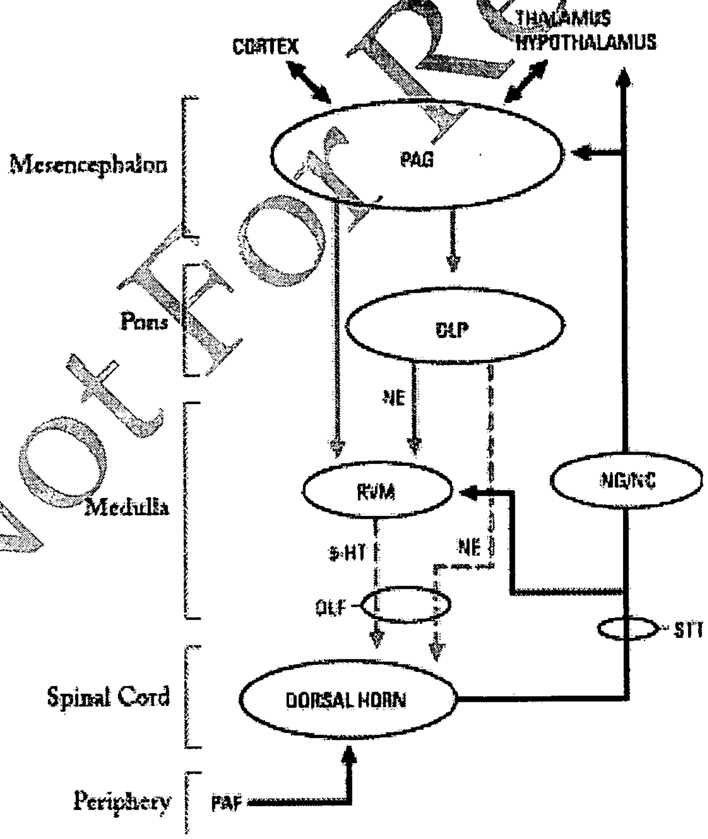
As shown in Figure 3, the main excitatory transmitter from the PAF to the dorsal horn neuron is glutamate (Glu) acting at several postsynaptic receptors, including those of the N-methyl-D-aspartate (NMDA) variety. In addition, neurokinins including substance P (SP),

FIGURE 2

The Ascending and Descending Pain Pathways

The ascending and descending pathways are shown in black and gray, respectively. The periaqueductal gray (PAG) represents a central structure in this system, processing both ascending and descending nociceptive information and linking higher-brain structures (including the thalamus and cortex) with the dorsal horn. Nociceptive input from the periphery is relayed via peripheral afferent fibers (PAF) to the dorsal horn of the spinal cord. After significant local processing, signals are relayed to higher centers via the spinothalamic tract (STT) to the nuclei gracilis and cuneiformis (NG/NC) and then on to the thalamus. The PAG has excitatory connections (shown in solid gray) to the rostral ventromedial medulla (RVM) and dorsolateral pontine catecholamine cell groups (DLP). The former is the primary source of spinal serotonin (5-HT), which, in turn, is primarily inhibitory at the level of the dorsal horn (dashed gray line). The DLP represents the major source of descending inhibitory norepinephrine (NE) spinal innervation. The 5-HT and NE pathways descend

Not For Reprint



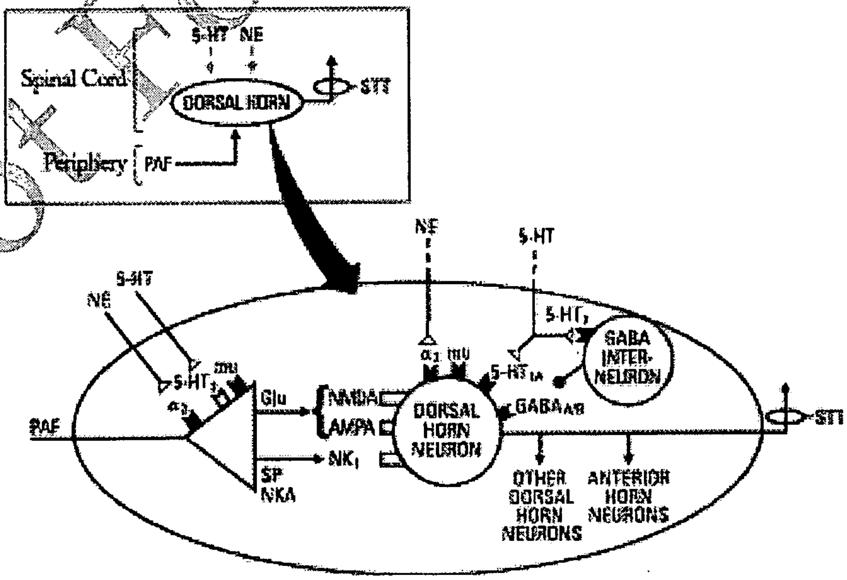
Kranzler JD, Gendreau JF, Rao SG. *Psychopharmacology Bulletin.* Vol 36. No 1. 2002.

calcitonin gene related peptide, and neurokinin A are colocalized with Glu. The descending pathways from the RVM and DLP, carrying 5-HT and NE, respectively, modulate the activity of the PAF terminals. For example, NE acting at α_2 receptors can inhibit the PAF terminal and cause a reduction in Glu and SP release, and a similar effect can be observed with activation of μ-opioid receptors located on the PAF ter-

FIGURE 3

The Dorsal Horn

The critical component at this level is the dorsal horn neuron, which receives input from the peripheral afferent fibers (PAF) and then projects both within the spinal cord and to higher centers via the spinothalamic tract (STT). The main excitatory transmitter from the PAF to the dorsal horn neuron is glutamate (Glu) acting at postsynaptic AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid), kainate, and NMDA (N-methyl-D-aspartate) receptors. In addition, neurokinins, including substance P (SP), calcitonin gene related peptide, and neurokinin A (NKA), are coreleased with Glu, and SP and NKA act via postsynaptic neurokinin-1 (NK_1) receptors. The PAF terminal itself receives modulatory input from a number of receptors, including α_2 and μ opioid (inhibitory, black), and $5\text{-}HT_3$ (excitatory, white). Activation of the inhibitory inputs causes a reduction in Glu and SP release, whereas $5\text{-}HT_3$ receptor activation causes enhanced release. The dorsal horn neuron is also subject to γ-aminobutyric acid (GABA), norepinephrine (NE), serotonin (5-HT), and opiate inhibitory input, acting respectively at $GABA_{A/B}$, α_2, $5\text{-}HT_{1A}$, and μ-opioid receptors. In particular, note that although 5-HT has an excitatory effect on the PAF terminals, it can inhibit the dorsal horn both directly (via $5\text{-}HT_{1A}$ activation) and indirectly (through activation of a GABAergic interneuron).



Kranzler JD, Gendreau JF, Rao SG. *Psychopharmacology Bulletin.* Vol 36. No 1. 2002.

minals. Conversely, 5-HT acting at 5-HT_3 receptors can increase the release of these neurotransmitters. Finally, increasing local 5-HT concentrations or α_2-mediated neurotransmission within the RVM itself has been shown to be antinociceptive.[42,43]

The dorsal horn neuron is also subject to noradrenergic, serotonergic, and opiate input, acting, respectively, at α_2, 5-HT_{1A}, and μ-opioid receptors. Note that all of these receptors are predominantly inhibitory, and, although 5-HT has excitatory effects on the PAF terminals, it can inhibit the dorsal horn both directly (via 5-HT_{1A} activation) and indirectly (through activation of a γ-aminobutyric acid [GABA]-ergic interneuron).

Chronic Pain: Changes in Nociceptive Processing

Over the past decade, it has been recognized that chronic pain is quite different, clinically and pharmacologically, from acute pain.[44] As described below, a number of alterations occurring both within the CNS and at the periphery may contribute to the chronic pain state. One can envision that disabling one or more antinociceptive pathways, or activating a pronociceptive one, can lead to a state of central sensitization. One such phenomenon that occurs at the PAF-dorsal horn neuron synapse is "wind-up." This term refers to a specific augmentation in the response of a dorsal horn neuron that results from tonic, peripheral nociceptive input, and such augmentation may underlie certain components of allodynia and hyperalgesia.[22,45,46] A number of studies suggest that the activations of NMDA and neurokinin-1 (NK_1) receptors represent critical steps in initiating wind-up and related phenomena in dorsal horn neurons.[45-52]

The descending systems also appear to play roles in central sensitization. For example, recent studies have demonstrated that reduced spinal NE outflow from the DLP results in a chronic hyperalgesic state in laboratory animals (L Jasmin, MD, PhD, FRCS, oral communication, August 29, 2001). Likewise, a significant body of research has implicated the RVM in maintaining the hyperalgesic state. For example, inactivation of the RVM (by lesion, injection of lidocaine, or spinal transection) can reverse the allodynia and hyperalgesia seen in animal models of chronic pain.[53] Further, the application of cholecystokinin-B receptor antagonists locally within the RVM reverses the mechanical allodynia observed in animal models of chronic neuropathic pain.[54] Finally, in addition to its role within the dorsal horn in initiating wind-up, direct injection of NMDA antagonists into the RVM is effective in reversing hyperalgesia caused by several chronic pain paradigms,[55-57] suggesting that NMDA receptors at the level of the RVM also play a role in maintaining a hyperalgesic state.

Laboratory Findings in Fibromyalgia Syndrome Patients

Like the study of many psychiatric diseases, the study of FMS is hampered today by the lack of well-validated animal models that can serve as proxies for the study of the disease in humans. Incidentally, great strides are being made in this regard by a number of researchers who are developing animal models of primary and secondary allodynia[58,59] (also, L Jasmin, MD, PhD, FRCS, oral communication, August 29, 2001). In the meantime, based on an understanding of normal physiology and armed with clues from similar diseases in humans, much insight can be gained from monitoring the status of biochemical pathways or physiological processes that may be affected in the disease process. A focus on the former, such as measurement of neurotransmitter levels in cerebrospinal fluid (CSF), facilitates the design of experiments that are relatively simple and subject to control, with the outcome providing a direct link to a drug discovery target. The results from any single analysis, however, may be difficult to interpret and will represent only one piece of a dynamic puzzle at a single point in time. In contrast, tests of physiological function, such as brain imaging or sleep lab monitoring, provide a more integrated perspective, but the data obtained may be of less practical use for the discovery or development of pharmaceutical compounds.

Although there are hundreds of papers in the literature attempting to identify quantifiable, objective, and meaningful biological differences in FMS patients, many are designed as pilot studies and lack sufficient power or controls to be conclusive. Therefore, we will limit our focus in this review to those findings that have achieved a critical mass of published data and that may be of interest to the psychiatric community. On the biochemical side, we will summarize the changes in neurotransmitter function and neuroendocrine status in FMS patients; we will then review the data garnered from more "functional" assays, including sleep lab and brain-imaging analyses in FMS subjects.

Neurotransmitter Function in Fibromyalgia Syndrome

Many of the assays developed by previous efforts to dissect the roles and relationships of various neurotransmitter systems in human psychiatric disease have been employed in the study of FMS. Although various investigations have examined a potential role for many of the known monoamine and peptide neurotransmitters in FMS,[60-62] most current knowledge concerns alterations in 5-HT and SP in affected patients. In general, the available data suggest a possible decrease in serotonergic activity in FMS patients and support an increase in SP as associated with the disease. Each of these observations, along with supporting data and potential implications, will be discussed in turn.

Changes in Serotonin—Given the central role of 5-HT in mediating many of the pathways that are clinically compromised in FMS, it is not surprising that 5-HT was the first neurotransmitter hypothesized to be involved in the disease.[63] Evidence for involvement of 5-HT in FMS has recently been reviewed by Alnigenis and Barland.[64] As described previously, the serotonergic descending inhibitory pathways can alter the sensation of pain. Another common symptom in FMS patients, fatigue, may also involve serotonergic pathways through a number of different mechanisms, including, but not limited to, the role of 5-HT in regulating the hypothalamic-pituitary-adrenal (HPA) axis,[65] elaborated upon in greater detail later in this article. Sleep disturbances, reported by the majority of FMS patients, may also implicate 5-HT, due to its central role in the regulation of sleep-wake cycles.[66] Finally, the frequent comorbidity of psychiatric conditions, such as depression, in FMS patients further supports a disturbance in monoamine function, particularly 5-HT.

Attempts to confirm an abnormality in 5-HT neurotransmission have measured levels of 5-HT, its precursor tryptophan, and its metabolites 5-HTP and 5-HIAA, in the blood, CSF, and urine of FMS patients. As only 1% to 2% of 5-HT is found in the brain (with the rest derived from platelets, mast cells, and enterochromaffin cells of the gastrointestinal tract), the most consistent results regarding alterations of 5-HT function in FMS are derived from sampling CSF. Although 5-HT levels were not measured directly, both Houvenagel et al[67] and Russell et al[61] reported decreased levels of 5-HIAA in the CSF of FMS patients versus controls. In the former study, controls included patients with lower back pain as well as pain-free subjects, with significant separation in both cases. No correlation between degree of pain and 5-HT levels in FMS patients was documented. A more recent study by Legangneux et al[68] was only able to replicate this difference in CSF 5-HIAA levels in female FMS patients versus controls; the small number of male subjects in the study precludes drawing any definitive conclusion.

In peripheral blood, there have been several studies in which researchers looked, with variable results, at tryptophan levels in FMS patients.[64] Of greater interest are studies measuring 5-HT levels. In these studies, too, the results are not entirely consistent, yet, most of these researchers find lower levels of 5-HT in the serum of FMS patients as compared with normal controls. In one report, serum and platelet 5-HT levels were demonstrated to correlate.[62] A significant inverse correlation between serum 5-HT level and the number of tender points in FMS patients was noted by Hrycaj et al,[69] who compared FMS patients with RA patients and normal controls. Similarly, Ernberg et al[70] found lower serum 5-HT levels in FMS patients than in RA patients. They speculated that the lower serum 5-HT levels in FMS were the result of increased platelet activation in these patients, leading to release of 5-HT into the plasma fraction of the blood, whereupon some of that 5-HT is sequestered by binding to nociceptors. Indeed, the researchers found that a high plasma-to-serum 5-HT ratio was associated with orofacial pain and anxiety in FMS patients. However, the authors' results and explanation are in conflict with the recent findings of Legangneux et al,[68] who reported higher levels of 5-HT in FMS samples versus controls despite using platelet-rich plasma as the source for assay.

The lack of consistency in the measurement of compounds related to 5-HT in body fluids is not surprising because such variability also has been the case in the attempt to document reduced 5-HT in depression, even within the CSF.[71] In fact, the selective serotonin reuptake inhibitors (SSRIs), which increase 5-HT centrally, lead to decreased CSF 5-HIAA, presumably because of feedback inhibition as a result of increased 5-HT within the synaptic cleft.[72] It has been suggested that CSF 5-HIAA is most reflective of 5-HT activity in the prefrontal cortex, based on analyses of postmortem samples of suicide victims.[73]

In contrast to CSF 5-HIAA levels, the measurement of reduced 5-HT uptake by platelets has proven to be a consistent marker for melancholic depression as has, to a lesser extent, the measurement of 5-HT transporter binding.[74,75] To date, however, results of the research experience directed at these two measurements in FMS patients has not been satisfying. We have not found any published studies of 5-HT uptake in FMS patients, and multiple attempts to identify changes within the 5-HT transporter by measurement of platelet [$_3$H] imipramine or [$_3$H] paroxetine binding have yielded conflicting results, from higher[76] to lower[77] to the same[68,78] as controls. A possible association of the syndrome with a polymorphism in the 5-HT transporter gene regulatory region has surfaced in genetic studies of FMS patients.[79] FMS patients in this cohort had a significantly higher distribution of the S/S genotype (homozygotic "short allele," consisting of a 44-basepair insertion in the transcriptional region of the 5-HT transporter gene), which is associated with decreased 5-HT transporter messenger RNA transcription and decreased 5-HT uptake capacity in vitro. These patients also had higher mean levels of depression and psychological distress clinically than did controls.

In summary, the body of published data, while providing some interesting clues, is not sufficient to either support or reject the hypothesis that there is a dysregulation of 5-HT metabolism in FMS. In both serum and CSF samples the assays performed of 5-HT levels and/or their precursors and metabolites, as well as of platelet [$_3$H] imipramine or paroxetine binding (representing 5-HT reuptake sites), are often variable in their reported results from different laboratories using similar techniques. Although it may very well be possible in some cases to reconcile the different results, the analogy to depression (which prompted much of this work at the outset) does not provide much comfort that this will be the most productive avenue of research. Specifically, although the monoamine hypothesis of depression was suggested more than 30 years ago, and despite an extraordinary amount of effort and resources having been devoted toward collecting data to establish a direct link between neurotransmitter dysregulation and depression, the goal remains elusive. In hindsight, given the complexity of the clinical presentation of depression and the neurotransmitter circuitry possibly affected, it is not surprising that, even if a discrete neurotransmitter defect were to exist, it may very well be masked when measured systemically. Arguably, because depression may appear as only one of the multiple symptoms within the FMS complex, the task of sorting out cause and effect within a single neurotransmitter system may prove even more formidable for FMS.

Changes in Substance P—SP is an 11-amino-acid neuropeptide thought to be involved in nociception.[80,81] It is found in both small, thinly myelinated *A*δ afferents and nonmyelinated *C*-fiber afferents terminating in the dorsal horn of the spinal cord. Direct application of SP to dorsal horn sensory neurons causes slow and prolonged excitation, similar to the response elicited by noxious stimuli. It has been suggested that SP acts as a neuromodulator, via the NK$_1$ receptor, sensitizing the neurons to the effects of other excitatory neurotransmitters.[82] Because of its presumed role in pain transmission, multiple studies have attempted to document changes of SP in chronic pain states.

In contrast to the 5-HT study results, the differences described regarding SP in FMS have been reproduced by multiple groups. Although SP levels in serum and urine of FMS patients have been reported as normal,[60] levels of SP in the CNS of FMS patients have been found to be consistently high in four different studies.[62,83-85] In all of these, the SP elevation in CSF was 2- to 3-fold greater than that found in normal controls, with little overlap between the values of the two groups.

However, the significance of these results and their relationship to FMS pathophysiology remain unclear. Russell,[60] based on unpublished data, has suggested that there is a trend toward correlation of CSF SP levels and pain severity in FMS patients over time. The source of the increased SP levels is unknown. Although it was anticipated that CSF SP would derive, primarily, from diffusion of neuropeptide released by afferent nerve fibers into the dorsal horn,[86] no increase in lumbar-level CSF SP could be induced by noxious pressure on the lower-body tender points, which would be expected to stimulate the primary afferents.[62] This result is inconsistent with extensive animal work that demonstrates release of SP into the dorsal horn in response to noxious stimuli[87-89] and, therefore, bears repetition. Significant concentrations of both SP and NK_1 receptors are found in other areas of the brain, including the striatum, hippocampus, raphe nucleus, and lateral nucleus of the hypothalamus.[90] However, it is difficult to definitively characterize the increased CSF levels of SP as secondary to increased brain levels because it is known that the brain stimulates the release of 5-HT in the spinal cord, which, in turn, decreases the release of SP into the spinal cord.[91-93]

It is of interest that, although high CSF levels of SP have been reported in trigeminal neuralgia,[94] other chronic pain states, including low back pain and painful diabetic neuropathy, are accompanied by low levels of CSF SP and/or monoamines, including 5-HT.[95-97] Clearly, proposing a one-fit model, such as wind-up, to apply to all chronic pain disorders is too simplistic to fit the full complement of data collected to date. Nevertheless, as the single most concrete neurochemical difference identified to this point in FMS patients, the high CSF concentrations of SP must be taken into account in any future investigation of mechanisms underlying FMS. Moreover, the potential inverse relationship between 5-HT and SP should be explored further. In this regard, Schwarz et al[98] reported a clearer result in serum, in which, despite normal levels of SP and 5-HT, a strong negative correlation could be documented between SP and both the 5-HT precursor tryptophan and the 5-HT metabolite 5-HIAA. Furthermore, in these experiments high serum 5-HIAA and tryptophan levels showed a significant relation to low pain scores, whereas high 5-HIAA levels were related to good sleep quality and high SP levels were related to sleep disturbance.

Neuroendocrine Changes

The HPA axis serves as the link between a stressor, such as pain, and an individual's endocrine, autonomic, and behavioral responses. Classically, the HPA axis is regarded as a system programmed to react to changes in the environment by producing chemical messengers that mediate physiological changes to maintain homeostasis.[99] However, recent evidence complicates this simple model by suggesting that genetic influences, environmental factors early in life, and exposure to chronic stress can permanently affect the HPA axis and predispose to the development of disease. Although much of this work has been done in the context of understanding the contribution of these changes to the pathophysiology of affective disorders,[100] similar mechanisms are believed to be operative in FMS.[101]

The key mediator in the HPA cascade is corticotropin-releasing hormone (CRH), a neuropeptide produced in the paraventricular hypothalamus in response to physical or psychological stress. CRH, in turn, stimulates the release of adrenocorticotropin hormone (ACTH) from anterior pituitary cells, which prompts the secretion of glucocorticoids from the adrenal gland to elicit adaptive reactions to the perceived threat, such as increasing blood glucose levels.[101] CRH can also exert secondary inhibitory effects on growth hormone (GH) and thyroid-stimulating hormone by functioning as a neurotransmitter, increasing the secretion of somatostatin from hypothalamic and cortical neurons[102] and causing hypothalamic LHRH (leutenizing hormone releasing hormone) secretion.[103] Simultaneous to activation of the HPA axis, an organism will react to stress with a "fight or flight" response, mediated by the autonomic nervous system and resulting in physiologic changes such as tachycardia and hypertension.

Despite the complexity of both the neuroendocrine feedback loops and the disease in which they are being studied, there is general consensus on the status of the HPA axis in FMS patients, as documented within the literature. The observations made in FMS include (1) normal to slightly elevated basal blood cortisol with blunted diurnal variation and resistance to suppression by dexamethasone[104]; (2) low to normal 24-hour urine cortisol[105] (also, LJ Crofford, MD, oral communication, September 10, 2001); (3) normal cortisol response to ACTH challenge but blunted cortisol response to CRH challenge[105-107]; (4) normal basal ACTH[101]; (5) exaggerated ACTH response to CRH challenge[105-107]; (6) decreased insulin-like growth factor (IGF-1)[108]; and (7) reduced thyrotropin response to exogenous thyrotropin-releasing hormone.[109] In addition, the autonomic nervous system of FMS patients is characterized by increased sympathetic and decreased parasympathetic tone, as evidenced by exaggerated changes in blood pressure and heart rate with postural change.[110] There is disagreement, however, as to the interpretation of these findings.

Neeck and Crofford[101] interpret this profile as representing hyperreactivity of the HPA axis secondary to chronic stress and the resulting increase in CRH activity. This interpretation is analogous to melancholic depression, in which a similar pattern of hypercortisolemia, sympathetic nervous system activation, and inhibition of growth and thyroid function have been demonstrated,[111] albeit with a diminished ACTH response to CRH stimulation.

In contrast, Torpy et al and Heim et al[113] interpret these very same findings as supporting decreased CRH neuronal activity in FMS, and they argue that the paucity of CRH's known antinociceptive effects through activation of arcuate nucleus pro-opiomelanocortin neurons may contribute to the hyperalgesia in FMS.[52] In this model, the dysautonomia in FMS is attributed to lack of stimulatory input by CRH neurons to central control nuclei (A1, A2, A6) within the DLP of the sympathetic nervous system,[114] resulting in relative hypovolemia and an exaggerated NE response (see Figure 2).

Surprisingly, there has been no attempt as of yet to directly measure CRH in the CSF of FMS patients to provide evidence for choosing one model over the other. However, similar attempts in depressed patients have yielded conflicting results.[115] Control of CRH neurons is via stimulatory 5-HT–containing neurons projecting from the midbrain raphe,[65] stimulatory NE-containing neurons from the locus coeruleus,[116] and inhibitory SP-containing central neurons.[117]

Therefore, it is tempting to link the hypocortisolism model of FMS to reduced central 5-HT and/or NE or to increased central SP, consistent with Russell's previously cited work.[62] Likewise, the observed hypoactivity of the GH axis in FMS can be attributed to low levels of GH-releasing hormone, which, due to diminished direct stimulation by NE-containing neurons, must counterbalance and overcome the tendency of lower levels of CRH to increase somatomedin release.[112] In contrast, the hypercortisolism model of FMS accounts easily for the decreased levels of growth and thyroid hormones by a direct inhibitory effect of CRH on somatomedin release.[101] However, it is less simple to reconcile this model to the neurotransmitter results of Russell.[60] Neeck and Crofford[101] suggest that the answer may lie in differentiating short-term versus longer-term effects of neurotransmitters on the HPA axis. For example, although citalopram, an SSRI, increases HPA activity in the short-term (presumably by a direct stimulatory effect of 5-HT on CRH release), longer-term treatment with citalopram desensitizes the HPA axis, consistent with its antidepressant effect.[118] Similar results have been reported with desipramine, a tricyclic antidepressant (TCA) and NE reuptake inhibitor,[118] with the long-term desensitization effect of NE on the HPA axis presumed to result from increased central sensitivity to the feedback of corticosteroids.

In summary, as the field has progressed and as investigators have learned to parse the neuroendocrinology findings specific to FMS from the ongoing processes of CFS, depression, and other disorders that often coexist in FMS patients, some clarity is emerging regarding the profile of the HPA axis in FMS. Areas of uncertainty, such as the role of CRH, will be further clarified by the use of CRH-modulating drugs[119] as biological probes, which may lead to potential therapeutics for FMS. Whether the characteristic hormonal profile of FMS is involved in the pathophysiology of the disease or is a reflection of the patient's symptoms remains to be determined.

Alterations in Sleep

In addition to pain and fatigue, nonrestorative sleep is a common problem in FMS and is reported to occur in more than three quarters of patients.[120-122] Sleep electroencephalography has demonstrated a number of abnormalities in the sleep architecture of FMS patients, including prolonged sleep latency, low sleep efficiency, a reduction in slow-wave sleep (SWS), an increase in alpha (stage 1) sleep, and an increased number of awakenings.[122-126] A fairly common finding in FMS patients is the presence of so-called "alpha-delta" sleep abnormalities—the presence of alpha waves during SWS—that appear to correlate with increased vigilance.[122,127-129] Other associated sleep problems seen commonly in FMS patients include periodic limb movements and sleep apnea.[123,130,131]

Sleep abnormalities, of course, are not specific to FMS; they also are seen in other chronic pain conditions[124,132] and in depression.[133] In fact, it has been shown that sleep deprivation in normal individuals can result in a myalgic syndrome that resembles FMS.[134-137] This finding has led to the hypothesis that sleep abnormalities may play a causal role in FMS pathophysiology.[134,137,138]

The initiation and regulation of the sleep state is quite complicated, with a number of midbrain and pontine serotonergic, noradrenergic, and cholinergic nuclei playing a role.[138] Thus, it comes as no surprise that agents that affect neurons within these nuclei or neurotransmitter systems also may have profound effects on sleep. Such agents include antidepressants, benzodiazepines, and γ-hydroxybutyrate; agents that augment SWS may be particularly beneficial.[133,139] As discussed elsewhere, all three classes of agents have been tested, with varying degrees of success, in FMS. However, studies correlating drug therapeutic effects with alterations in sleep architecture have been limited and, so far, remain inconclusive.[140]

Neuroimaging Studies

Several studies have utilized functional imaging to investigate abnormalities in CNS function in FMS patients.[19,141-144] Two of these studies used single-photon emission computed tomography (SPECT) imaging,[19,141] and one used positron emission tomography (PET).[143] These techniques are similar, employing radioactive tracers to measure regional cerebral blood flow (rCBF) in brain areas of interest. Currently, the main difference between these technologies is that PET uses radioactive tracers with a shorter half-life than SPECT, which results in improved temporal resolution.[145] In contrast to SPECT and PET, Petzke et al[144] utilized functional magnetic resonance imaging (fMRI), a technique that directly tracks local changes in blood flow through changes in water molecule density.[146] Of the three techniques, fMRI has the highest spatial and temporal resolution.[146]

The study by Mountz et al[19] found bilateral hypoperfusion of the thalamus and head of the caudate nucleus in 10 women with FMS as compared with 7 age- and education-matched controls. Concerns regarding this study (beyond its small size) were the medication status and psychological state of the patients. Based on self-reports, patients discontinued their medications 4 days prior to the initiation of the study. The serum half-lives, however, of some of the medications, including fluoxetine and amitriptyline, are measured in days[19,147]; thus, significant serum levels of such medications were probably present in some patients at the time of their scans. More importantly, the patient population appeared significantly more depressed and/or anxious (per the Center for Epidemiological Studies Depression Scale and the Trait Anxiety Inventory, respectively) than the controls.[19]

Some of these concerns were addressed in a recent SPECT study[141] aimed at confirming and extending the results of Mountz et al.[19] This study evaluated a total of 17 patients and 22 controls (all women). At the time of the study, 10 of the FMS patients were taking antidepressants, benzodiazepines, and/or narcotics. The remaining seven patients were not taking any medications within these classes. Once again, however, the FMS patients were significantly more depressed and/or anxious than were their control counterparts. The results did confirm that rCBF in FMS patients is abnormal; however, statistically significant changes were only found in the right thalamus (the reductions in rCBF seen in the left thalamus did not reach statistical significance). The authors were also unable to confirm the bilateral changes in the heads of the caudate nuclei, as had been found by Mountz et al.[19] Finally, additional abnormalities in the inferior pontine tegmentum were noted. The results for patients not taking medications were similar but less significant; it is not clear whether this reduction in significance was a result of differences in neuropharmacology or due to smaller sample sizes.

Taken together, these studies suggest that FMS patients may have reduced rCBF in one or both thalami. Studies in other forms of chronic pain have also found decreases in thalamic rCBF, and these changes may reverse when the pain is alleviated.[148-151] A concern with the Mountz et al[19] and Kwiatek et al[141] studies is a lack of control for concomitant depression and anxiety. Patients with such conditions who do not have FMS also show abnormalities in rCBF,[152,153] although the overall patterns appear different from those found in the two studies just described. Finally, the possibility of rCBF abnormalities in the inferior pontine tegmentum is tantalizing, as a number of nuclei with descending inhibitory effects on nociception are located in and around this region, as described previously (Figure 2).

Of particular interest from a pathophysiological perspective is the work of Petzke et al,[144] who used the fMRI imaging modality to investigate differences in cortical activation between 16 FMS patients and 16 controls while they underwent pressure-pain testing (thumbnail pressure). Each FMS subject had an fMRI performed while being subjected to "moderately painful" pressure, as defined by the Gracely Scale.[154] The control subjects were scanned under two conditions: the "stimulus pressure control" condition and the "subjective pain control" condition. The former referred to testing the controls with the same level of mechanical pressure as used on the FMS patients, whereas the latter involved scanning the controls when they, like the FMS patients, reported moderate pain. It was found that the levels of cortical activation between the FMS patients and the controls under the subjective pain control condition were similar. However, fMRI scans of control subjects under the stimulus pressure control condition showed no significant activation. These results are strongly supportive of alterations in the threshold and gain of the nociceptive system in FMS patients and are consistent with a model of central sensitization. Note that although data regarding the effects of psychological state on fMRI results were not presented, this lack of data presents less of a concern in fMRI than in PET or SPECT scans, as a change from baseline within the same patient is being measured.

Clinical Pharmacology of Fibromyalgia Syndrome

The investigation of therapeutics specifically for FMS has tended to lag several years behind studies for other chronic pain conditions. With the exception of a significant body of literature pertaining to the use of TCAs, only a handful of randomized controlled trials have been published evaluating the efficacy of other proposed therapeutic agents in FMS. In addition, FMS has not received much attention from the pharmaceutical industry, and no medication currently holds an approval specifically for this indication. Without the pressures intrinsic to the regulatory approval process, no consensus has been reached regarding many aspects of trial design, including designation of endpoints. Since no binary definition of a "responder" versus a "nonresponder" exists for FMS drug trials as it does for certain other rheumatological conditions such as RA,[155,156] debate continues regarding which endpoints are optimal. For example, even though there is general agreement that the measurement and characterization of patients' pain is of paramount importance, there are differing opinions regarding which measurement tools are best suited for this purpose. And although there is general agreement that assessments of fatigue, sleep, depression, physical functionality, and overall well being are all important, it is not clear how to integrate all of these data into a composite determination of efficacy or a definition of response. A syndrome-specific tool introduced in 1991, the Fibromyalgia Impact Questionnaire (FIQ), is one of many efforts to standardize the measurement of patients' responses to interventions.[157] The FIQ is a relatively brief, 10-item, self-administered tool designed to evaluate physical functioning, work status, depression, anxiety, sleep, pain, stiffness, fatigue, and overall well being, and, although it has been used frequently as an outcome measure, no consensus exists regarding its validity as a stand-alone primary endpoint. Another tool that has been utilized often in FMS studies is the short form of the McGill Pain Questionnaire.[158,159] Through the use of various pain descriptors, such as "aching" and "exhausting," this instrument appears to be quite sensitive to changes experienced by FMS patients undergoing treatment. It is not a disease-specific instrument, however, and like the FIQ, it is not used universally within the FMS clinical research community.

Compounding the impact of these factors, a large percentage of the existing clinical data is derived from relatively small studies, and high dropout rates and placebo response rates have often compromised the statistical power and significance of these results.[160,161] Trials have also tended to be of short duration, and there is very limited information regarding the long-term efficacy of any of the agents currently used in the treatment of this chronic condition.

Other trial-related issues deserve mention as well. Although the 1990 American College of Rheumatology criteria for the classification of

FMS have helped standardize the identification of patients appropriate for entry into clinical trials,[4] the patient population remains extremely diverse and heterogenous. In addition, most of the published trials have enrolled predominantly tertiary care patients—patients who tend to be the most refractory to available therapies.[25] Therefore, these data may not accurately reflect the characteristics of the FMS population as a whole, which includes a large percentage of less severely impaired patients treated in primary care settings.[4,162]

The issue of comorbid depression and its impact on patients' responses to therapeutic interventions is also critical in the design of FMS trials. Standard practice has been to exclude patients with severe psychiatric illness from clinical trials by way of incorporating psychometric instruments such as the Hamilton Rating Scale for Depression, the Montgomery-Asberg Depression Rating Scale, or the Beck Depression Inventory as prescreening tools.[163-167] However, a great deal of additional information is required before the complex interrelationships between depression, pain, and other symptoms of FMS can be ascertained.

The Fibromyalgia Syndrome Pharmacopoeia

A broad array of medications are used to treat patients with FMS, with varying degrees of success.[168-171] Although antidepressants are the cornerstone of current treatment paradigms, many other agents within the standard armamentarium of the psychiatrist have been employed in the management of FMS patients, including anticonvulsants, antispasticity agents, anxiolytics, sedatives, and opiates. Nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen also are used by a large number of patients,[172] even though peripheral inflammation has not been demonstrated,[15] and numerous studies have failed to confirm their effectiveness as analgesics in FMS.[173-177] They do, however, provide an element of protection against other peripheral pain generators, such as OA, and there is limited evidence that patients may experience enhanced analgesia when treated with combinations of NSAIDs and other agents.[173,176,177]

In this section, we have chosen to review briefly a number of the many agents that have been employed to treat FMS. A drug was included if it met one or more of the following criteria:

1. There exists a large quantity of clinical data for the use of the agent in the treatment of FMS, eg, TCAs, SSRIs, and 5-HT_3 receptor antagonists.
2. The approach is based on solid preclinical scientific data, eg, NK_1 antagonists, NMDA antagonists, and GH.

3. The drugs have other uses in psychiatry, eg, mood stabilizers or antiepileptic drugs (AEDs), atypical antidepressants, anxiolytics, hypnotics, and α_2-adrenergic agonists acting as antispasticity agents, such as clonidine and tizanidine.

Some of these drugs can be supported as primary therapy. Others may have an adjuvant role in addressing symptoms other than pain and may be important in the overall management of these patients. For example, anxiolytics and hypnotics, which have not been shown to be effective as analgesics, may provide clinically meaningful relief of symptoms related to sleep disturbances, anxiety, and fatigue, thereby improving overall well being.[168,177-179] A review of commonly used agents, segregated by pharmacological classification, follows.

Antidepressants

Antidepressants of all varieties represent a common form of therapy for many chronic pain states, including FMS.[21,168-171] The majority of available antidepressants directly and/or indirectly increase the levels of 5-HT and/or NE in the CNS. Monoaminergic levels are increased either by inhibiting reuptake (by blocking transport proteins) or by interfering with the breakdown of the monoamine after its release into the synaptic cleft (by inhibiting the monoamine oxidase [MAO] enzymes). As previously discussed, 5-HT–mediated antinociceptive effects have been localized to the level of the dorsal horn (mediated by both direct and indirect effects) and to the level of the RVM. NE-mediated neurotransmission has antinociceptive effects at the level of the dorsal horn and PAF.

Although current classification schemes have tended to segregate agents based on their in vitro effects on 5-HT and NE reuptake activity, agents within a given class vary significantly in terms of their relative in vitro and in vivo actions (see Table 2).[147,180-183] And although the optimal combination of 5-HT and NE modulation is not well defined for FMS, the results of studies of other chronic pain conditions has, in general, indicated that antidepressants having both serotonergic and noradrenergic actions have a more consistent antinociceptive effect than do SSRIs.[184] They also suggest that a shift toward greater noradrenergic enhancement may be critical for optimal analgesic effect.[185]

Tricyclic Antidepressants—The TCAs most commonly employed in the treatment of FMS include amitriptyline, doxepin, and cyclobenzaprine.[168,170,171] Although cyclobenzaprine is typically classified as a muscle relaxant rather than an antidepressant, it shares structural and pharmacological similarities with the TCAs, even though its sedating qualities often override its usefulness in other applications.[186] TCAs block the reuptake of both 5-HT and NE, but they favor NE reuptake blockade, with the ratio of K_i for NE reuptake to K_i for 5-HT reuptake ranging from 1.6 for amitriptyline to 168 for nortriptyline (Table 2). Amitriptyline (with a half-life of 12–36 hours) is metabolized primarily to nortriptyline (with a half-life of 22–88 hours),[147] further adding to the NE bias, especially at the lower dosages that have been used historically to treat chronic pain. The efficacy of TCAs, therefore, can be interpreted to support the primacy of NE agonism for analgesic activity. Beyond increasing NE and 5-HT levels, TCAs have other important pharmacologic properties, including dopamine reuptake inhibition, NMDA antagonism, and ion-channel blocking activity.[187-194] Therefore, there is overlap between the mechanisms of action (ie, ion-channel blockade) of the tricyclics and other agents such as antiepileptics. TCAs' additional anticholinergic, antihistaminergic, and α-adrenergic receptor blockade activities impart a wide assortment of undesirable

TABLE 2

Comparison of Monoamine Reuptake Inhibitory Activity (IC_{50})

The IC_{50}s of a number of antidepressant agents from the TCA, SNRI, and SSRI classes are presented to differentiate drugs on the basis of their relative selectivity for NE and 5-HT. Some of the SNRI data are from different sources than those of the other agents, so several references are provided for comparison, particularly because a variety of in vitro techniques were used by the various authors in generating this data.

Class	IC_{50}			
AGENT	NE (nM)	5-HT (nM)	RATIO (5-HT:NE)	REFERENCE
SNRI				
Milnacipran	100	203	1:2	Moret et al[180]
	31.4	61.8	1:2	Palmier et al[181]
Duloxetine	46	28	1.6:1	Kasamo et al[182]
	7.5	0.5	15:1	Bymaster et al[183]
Venlafaxine	640	210	3:1	Sanchez and Hyttel[147]
	2483	82	30:1	Bymaster et al[183]
TCA				
Amitriptyline	24	39	1:1.6	Sanchez and Hyttel[147]
Nortriptyline	3.4	570	1:168	Sanchez and Hyttel[147]
SSRI				
Fluoxetine	370	6.8	54:1	Sanchez and Hyttel[147]
Citalopram	6100	1.8	3400:1	Sanchez and Hyttel[147]
Paroxetine	81	0.29	280:1	Sanchez and Hyttel[147]

IC_{50}=dose at which 50% inhibition of neurotransmitter reuptake activity occurs;
TCA=tricyclic antidepressant; SNRI=dual reuptake inhibitor;
SSRI=selective serotonin reuptake inhibitor; NE=norepinephrine; 5-HT=serotonin.

Kranzler JD, Gendreau JF, Rao SG. *Psychopharmacology Bulletin.* Vol 36. No 1. 2002.

side effects, which often compromise the tolerability and clinical acceptance of this class of agents.[195]

TCAs have demonstrated moderate efficacy for the treatment of neuropathic pain conditions such as postherpetic neuralgia and painful diabetic neuropathy.[196-199] Multiple studies of TCAs in the treatment of FMS support their use in this syndrome as well, and TCAs have frequently been used as the positive controls with which newer agents have been compared.[196,199-202]

The results from TCA trials in FMS have been compiled and analyzed in two meta-analyses (Arnold et al[160] and O'Malley et al[161]) utilizing 9 and 13 antidepressant trials, respectively. In essence, the authors both concluded that TCAs provide "moderate" improvement in FMS, with the greatest impact on measurements of sleep, overall well being, and pain severity. Arnold et al[160] reported that significant clinical response to TCAs was observed in 25% to 37% of patients, whereas O'Malley et al[161] reported that patients receiving TCAs were "four times as likely" to report overall improvement (compared with placebo) and to experience moderate reductions in individual symptoms.

It is important to note that most trials have evaluated low doses of TCAs, typically below those used for antidepressant effects. Trial durations have also tended to be short—usually 6–12 weeks—with primary endpoints often obtained prior to the time when the maximal antidepressant response might be recognized. Although the antidepressant activity of these agents may contribute to the efficacy observed in certain patients, their role as centrally acting analgesics appears to be more critical. This premise is supported by results from trials of various SSRIs, which, in general, do not appear to be as effective analgesics as are the TCAs, even at doses with superior antidepressant activity.[196,203] Similarly, several studies have indicated that SSRIs often significantly improve depression but do not impact pain in patients suffering from both.[201,204]

Selective Serotonin Reuptake Inhibitors—SSRIs have revolutionized the treatment of depression with their improved side-effect profile secondary to more selective reuptake inhibition.[147,205,206] The SSRI agents fluoxetine, sertraline, and citalopram have each been evaluated in randomized, placebo-controlled trials in FMS.[200,201,204,207,208] The results of these trials have been inconsistent, leaving much debate regarding the relative efficacy of the SSRIs in FMS, especially in comparison with TCAs. The results from two controlled fluoxetine studies have now been published. The first of these, a double-blind, placebo-controlled crossover study comparing treatment with 20 mg fluoxetine, 25 mg amitriptyline, and the combination of both agents, concluded that there was significant efficacy with fluoxetine when compared to placebo and equivalent efficacy compared with amitriptyline.[201] This study also found that the combination of amitriptyline and fluoxetine was significantly more effective than either agent used alone, although whether this effect merely reflected higher blood levels of amitriptyline due to fluoxetine's effect on cytochrome P450 was not analyzed. The results of a second double-blind parallel group comparison of the administration of 20 mg fluoxetine and placebo were essentially negative, failing to show any significant improvement in pain, although mild improvements were noted in sleep and depression.[204] It should be noted that the statistical power of this study was impacted by a very high dropout rate and lower-than-anticipated enrollment, and that almost twice as many patients receiving placebo discontinued compared with those receiving fluoxetine.

Two placebo-controlled trials of citalopram, the most 5-HT–specific of the SSRIs (see Table 2), in FMS patients were both convincingly negative.[207,208] This suggests that serotonergic activity alone is not sufficient to effect analgesia in the chronic pain setting. In fact, the SSRIs are, as a class, generally less efficacious than the TCAs in chronic pain states, based on the evidence assembled to date,[185,196,209,210] although there are some exceptions.[211,212]

Considering both the TCA and SSRI findings, we would suggest the following:

1. Both noradrenergic and serotonergic activity can be antinociceptive in chronic pain states.[21,185,209,210]
2. The combination of positive results for TCAs (and maprotiline; see noradrenergic-specific reuptake inhibitors [NARIs] section) with the comparatively poor results for SSRIs in general, and citalopram in particular, suggest that 5-HT may play a secondary role to NE for an analgesic effect in chronic pain.[185] This is in contrast to depression, in which NE's role is generally considered to be secondary to that of 5-HT.[213]
3. The combination of NE and 5-HT is synergistic[201] and may be optimal for FMS treatment.

Dual Reuptake Inhibitors—The term "novel antidepressant" covers a great deal of pharmacological variety, including serotonin/norepinephrine dual reuptake inhibitors (SNRIs), NARIs, 5-HT receptor antagonists, monoamine oxidase inhibitors (MAOIs), and others.[195] Although several of these agents appear promising for the treatment of FMS, results from controlled studies for these newer antidepressants are generally not yet available.

SNRIs are pharmacologically similar to TCAs such as amitriptyline, exhibiting dual activity on 5-HT and NE reuptake.[147] Fortunately, these newer agents are generally devoid of significant activity at other receptor systems, resulting in diminished side effects and enhanced tolerability. Therefore, this class of antidepressant may have significant potential for the treatment of FMS and/or other chronic pain conditions.

Venlafaxine is the only SNRI currently available in the United States, although several others are in various stages of clinical development.[214,215] Although randomized, controlled studies are still lacking, one small, open-label trial of venlafaxine in 15 patients with FMS showed promising results.[216] Six of 11 patients who completed the trial had a positive response to venlafaxine, defined as 50% or greater improvement in two different measurements of overall pain. Insomnia was the most common side effect reported, requiring adjunctive medical therapy in 3 of 11 completing patients.

Based on the trends extrapolated from the TCA and SSRI data, it would be expected that venlafaxine's efficacy in FMS would be dependent, at least in part, on its reported NE activity. However, there are recent data suggesting that venlafaxine is primarily a 5-HT reuptake inhibitor at lower doses, with NE effects apparent only at high doses, ie, 375 mg/day,[217,218] which is significantly higher than the mean final dose of 167 mg/day reported in the FMS trial of Dwight and colleagues.[216] The inability of Harvey et al[217] to document in vivo NE reuptake blockade with low-dose venlafaxine may reflect their utilization of a blood pressure response to infused tyramine as the assay for readout of NE activity. More recently, Gilmour, Owens, and Nemeroff (unpublished data, 2001) developed an assay incorporating the cloned NE transporter gene transfected into HEK-293 cells.[219] Using this more sensitive assay, this group was able to demonstrate NE reuptake blockade ex vivo with paroxetine at antidepressant doses at which in vitro binding to the NE transporter cannot be measured. It would be expected that, were this protocol repeated for venlafaxine, significant inhibition of NE reuptake might be detected at doses approximating those administered by Dwight et al[216] to FMS patients.

A second SNRI, duloxetine, an agent similar to venlafaxine with relatively more inhibition of 5-HT reuptake than NE, is also in clinical development, and the results of FMS and depression studies are pending. Milnacipran, another SNRI, has been approved for treatment of depression since 1997 in Europe and elsewhere, but it has not been registered in the United States.[220] Unlike venlafaxine and duloxetine, and similar to the TCAs, milnacipran is the only SNRI with a preference for NE. In addition to its dual 5-HT/NE reuptake inhibition within its therapeutic dose range,[181] milnacipran also exhibits mild NMDA inhibition[221]; however, the significance of this activity and the drug's effectiveness in FMS or other pain conditions have not been formally studied. The relative doses at which 50% inhibition of NE and 5-HT reuptake activity occurs (IC_{50}s) are detailed in Table 2.[147,180-183] A range of results have been listed in the table for each of the SNRIs, as no head-to-head comparison has yet been performed between these newer compounds and the older SSRIs and TCAs listed. Because the ideal ratio between serotonergic and noradrenergic modulation required for optimal analgesic effect is not yet well defined, the comparative data from clinical trials of these agents should provide interesting insights.

Other Novel Antidepressants—Reboxetine, classified as an NARI due to its selective inhibition of NE reuptake, is licensed as an antidepressant in Europe. It is not available in the United States at this point, and studies into its analgesic effects in FMS or other chronic pain conditions have not yet been published. However, a randomized, double-blind, placebo-controlled trial in patients with chronic low back pain reported that maprotiline, a TCA agent similar to reboxetine in its relative specificity for noradrenergic reuptake inhibition, exhibited significantly greater efficacy than paroxetine at standard doses.[185] A different study, however, found maprotiline to be somewhat less effective than amitriptyline in the treatment of postherpetic neuralgia.[199] Therefore, the results of limited empirical studies as well as scientific considerations lead one to assume that the NARIs may exhibit better analgesic efficacy than the SSRIs, yet somewhat less efficacy than the TCAs and SNRIs, which influence both monoamines. Obviously, additional studies are required to confirm the role that these agents will play in the treatment of chronic pain.

There are no published studies on the analgesic capabilities of nefazodone, a $5\text{-}HT_{2A}$ receptor antagonist as well as a weak SNRI. Animal studies have suggested that its $5\text{-}HT_2$ antagonism may be antinociceptive, due to increases in $5\text{-}HT_{1A}$–mediated neurotransmission. The clinical relevance of this has yet to be determined, especially because a related molecule, trazadone, has failed to exhibit significant analgesic effects when used for various pain conditions, including FMS.[209]

Mirtazapine is a potent central α_2 autoreceptor antagonist as well as a $5\text{-}HT_2$ and $5\text{-}HT_3$ receptor antagonist with some anecdotal success as an analgesic.[222] Although no controlled studies have been reported, mirtazapine's α_2 autoreceptor-mediated increases in NE (as well as in $5\text{-}HT_{1A}$) neurotransmission and its ability to inhibit $5\text{-}HT_3$ (discussed below) may impart some antinociceptive activity.

Reversible Monoamine Oxidase Inhibitors—Nonspecific MAOIs, including phenelzine and tranylcypromine, have been on the market in the United States for many years, although concerns about potentially fatal interactions with certain foods and medications have limited their widespread usage. It is generally agreed that nonreversible inhibition of MAO-A is primarily associated with these adverse interactions.[223,224] Two new agents that selectively and reversibly inhibit MAO-A, moclobemide and pirlindole, have been approved recently in Europe. Early studies with moclobemide have generally demonstrated poor analgesic activity in neuropathic pain conditions, and preliminary experience with moclobemide in FMS has failed to demonstrate significant analgesic activity when compared with amitriptyline.[202,225] However, the results of a randomized, double-blind, placebo-controlled trial of pirlindole were more promising.[226] At this point, the data are insufficient to generalize as to whether reversible MAOIs, as a class, will have significant analgesic properties. The mixed results to date may reflect on the class as a whole or only on the particular molecules that have been developed. On purely theoretical grounds, it would be expected that reversible MAOIs would be effective analgesics, secondary to their inhibitory action on synaptic and extrasynaptic breakdown of both NE and 5-HT.

Opiates

As discussed previously, opiates exert antinociceptive effects at various locations within both the ascending and descending pain pathways. Morphine, a predominantly μ agonist, reduces transmitter release from the PAF terminals and reduces the activity of pronociceptive neurons within the RVM.[227-230]

Concerns pertaining to the use of narcotics in chronic pain conditions are widely discussed and are debated elsewhere.[171] However, narcotics are used by some healthcare practitioners in the clinical management of FMS, especially when other analgesics have failed to provide sufficient relief.[231] There is one particular agent that deserves special mention, namely tramadol. Although bothersome side effects preclude its successful use in a significant percentage of patients, tramadol has demonstrated efficacy in FMS,[232] as well as in painful diabetic neuropathy.[233] This unique agent combines opiate receptor agonist activity with monoamine reuptake inhibition, and recent research has suggested that it may also have agonist activity at the 5-HT_{1A} receptor.[234,235] As a result of its unique pharmacological profile, tramadol may exert its antinociceptive effects at locations within both the ascending and descending pain pathways.

Antiepileptic Drugs

The similarities between certain pathophysiological and biochemical mechanisms observed in epilepsy and neuropathic pain led to initial investigations of AEDs in chronic pain states.[236] Agents such as carbamazepine, lamotrigine, phenytoin, benzodiazepines, and gabapentin have been evaluated in neuropathic pain, and they have been shown to have analgesic effects to varying degrees.[237] As a result, a number of drugs initially labeled as antiepileptic agents are used regularly as analgesics.

The majority of AEDs increase seizure threshold by reducing neuronal excitability through sodium and/or calcium channel blockade, and this mechanism of action appears to underlie their analgesic activity as well.[237] In addition, agents such as benzodiazepines, tiagabine, valproic acid, and topiramate also enhance GABAergic neurotransmission.[238] Therefore, although each specific agent's mechanism of action may differ, AEDs, as a class, generally reduce excitability, decrease ectopic discharge, and reduce neurotransmitter release—effects that have been found to impart varying degrees of antinociceptive as well as antiepileptic activity.

Carbamazepine and gabapentin have been approved as first-line therapies for trigeminal neuralgia and painful diabetic neuropathy, respectively, and the effectiveness of gabapentin in diabetic postherpetic neuralgia has also been demonstrated.[239,240] Other anticonvulsants, such as topiramate and lamotrigine, have received recent attention for their potential efficacy in neuropathic pain conditions.[21,237,241-243] However, no clinical evaluation of the effectiveness of the AEDs in FMS has been published, and the discouraging side-effect profile of many of these agents has typically deterred their evaluation as front-line therapies.

Nevertheless, there are two structurally similar AEDs that are likely to undergo further evaluation in FMS due to their potential efficacy and relatively benign safety profiles, namely gabapentin and pregabalin. Gabapentin has been found to be efficacious in a variety of disorders ranging from bipolar disorder[244] to neuropathic pain,[245] and it may be particularly useful in pain states where hyperalgesia is present.[246] Some data suggest that gabapentin may also exhibit some anti-inflammatory qualities.[247] Pregabalin is still in clinical development, and, thus, efficacy studies are ongoing. Recently published results do suggest that pregabalin may be useful in treating such conditions as dental pain, postherpetic neuralgia, and painful diabetic neuropathy.[248-250] The mechanism of action of gabapentin is unknown, although its analgesic and anti-inflammatory activities may result from the agent's ability to block both calcium channels[251] and the induced release of Glu.[252,253] As reviewed by Bryans and Wustrow,[254] pregabalin probably possesses similar pharmacologic properties. In summary, although their utility in FMS has yet to be determined, both gabapentin and pregabalin appear to warrant further investigation.

Anxiolytic and Hypnotic Agents

Benzodiazepines are GABA agonists, having analgesic actions in the spinal cord and brainstem of animal models,[255] as well as antiepileptic properties (as described earlier) and muscle-relaxant properties (as discussed later). Although several uncontrolled studies have supported the benefit of clonazepam in trigeminal neuralgia, its use is compromised by side effects such as marked drowsiness or frank sedation.[256,257] In general, studies with other benzodiazepines in neuropathic pain have tended to be small and uncontrolled, and results have been inconsistent.[197] The available data are also limited in FMS, but, generally, these agents have been ineffective as analgesics.[176,177]

A handful of studies have been published on the use of certain nonbenzodiazepine hypnotics in FMS, such as zopiclone and zolpidem. These reports have suggested that, although they improve patients' subjective sleep complaints, these agents do not improve the pain of FMS.[178,179,258]

Researchers have attempted to elucidate the relationship between circadian rhythms, melatonin secretion, and FMS, with inconsistent results.[259-263] Melatonin, available in the United States as an unregulated dietary supplement, has been evaluated in one small, open-label pilot study involving 21 patients with FMS who were each given 3 mg of melatonin nightly for 30 days. Although this study suggested possible benefits in sleep and tender point counts, melatonin did not appear to impact patients' overall levels of pain or fatigue.[259]

Because γ-hydroxybutyrate has been reported to qualitatively improve sleep by increasing the quantity of SWS and decreasing α-intrusion without significantly changing the quantity of rapid eye movement (REM) sleep, it has been studied in a small, open-label trial in FMS. Although it appeared to improve sleep in some FMS patients, the clinical significance of these changes is unclear due to confounding variables such as allowance of concomitant medications.[139] In addition, the short half-life of γ-hydroxybutyrate required its administration twice during the course of the night, which also disrupted normal sleep architecture. Nevertheless, investigations that attempt to correlate changes in sleep architecture with clinical endpoints other than sleep may provide valuable information into the pathophysiology of FMS and the design of future therapies.

Antispasticity Agents

Tizanidine, an α_2-adrenergic agonist, reduces muscle spasticity by increasing presynaptic inhibition of motor neurons, and it has also demonstrated analgesic effects in animal pain models.[264,265] Clonidine is a related molecule with 10–50 times greater antihypertensive activity than tizanidine (hence marketed for this purpose) due to its higher affinity for imidazoline receptors involved in the central control of blood pressure, heart rate, and other metabolic functions, and it too has analgesic effects.[266] The antinociceptive properties of the α_2 agonists are not surprising when one considers the multiple sites of α_2-adrenergic receptors within both the ascending and descending pathways. For instance, α_2 stimulation reduces activation of PAF terminals, thereby reducing Glu and SP release. Increased α_2 stimulation within the RVM may also activate the descending 5-HT system, providing further antinociception. These agents also may directly inhibit dorsal horn projection neurons. Although controlled trials in FMS have yet to be performed, preliminary studies suggest that tizanidine may have efficacy in other chronic pain conditions, such as headache and low-back pain.[267-269] Side effects such as dry mouth, somnolence, and dizziness, although common, are usually manageable.

Baclofen is a $GABA_B$ agonist also approved as an antispasticity agent and, likewise, documented to be an effective adjuvant analgesic in the management of various types of neuropathic pain.[270-272] Although its mode of action is not fully characterized, its analgesic effects may result from suppression of dorsal horn neuronal activity. Currently, there are no data pertaining to the use of baclofen in patients with FMS.

5-HT_3 Receptor Antagonists

5-HT_3 receptor antagonists (such as ondansetron and tropisetron), best known for their antiemetic properties, also have analgesic effects.[273] Animal models have demonstrated that blockade of 5-HT_3 receptors has both pro- and antinociceptive effects, and clinical trials in settings of chronic pain have repeatedly revealed a bell-shaped dose-response curve, suggesting that optimal analgesic effect may involve a dose-dependent balancing act between these opposing activities. This duality of effect may be due, in part, to the presence of 5-HT_3 receptors on both PAF terminals and inhibitory dorsal horn interneurons, and it is an appropriate reminder of the complex ways in which the myriad 5-HT (and other) receptors interact throughout the pain pathways.[273-276]

Members of the German Fibromyalgia Study Group have extensively studied tropisetron in patients with FMS.[277-282] In addition to several small, open-label evaluations, a single randomized placebo-controlled double-blind trial investigated the effectiveness of 5 mg, 10 mg, or 15 mg of tropisetron given once daily for 10 days to 418 FMS patients. The results from this study suggested modest but statistically and clinically significant reductions in pain only in those patients treated with 5 mg of tropisetron, consistent with the earlier described bell-shaped dose response curve. Constipation and other gastrointestinal complaints were commonly reported, as with other 5-HT$_3$ blockers.

Miscellaneous Agents

NMDA receptor antagonists such as ketamine, dextromethorphan, and amantadine have antinociceptive action in animal models as well as analgesic qualities in humans[283]; however, their dose-limiting side effects have precluded their widespread use as therapeutic agents. Most of the available research has involved ketamine, a parenteral, dissociative anesthetic, and although this work has provided useful scientific data, this particular agent is not well suited for the management of chronic pain conditions such as FMS.[284,285] Dextromethorphan, a weak NMDA antagonist, is also hindered by side effects at the doses required to provide significant pain relief, but limited studies have shown it to be modestly effective in certain neuropathic pain conditions.[286,287] Although the search continues for agents with more tolerable side-effect profiles, they may ultimately prove to be most beneficial as adjunctive therapies when used concomitantly with other analgesics.[288]

Considering the observation that SP levels within the CSF of patients with FMS are routinely elevated, drugs designed specifically as SP or NK$_1$ receptor antagonists are theoretically attractive. However, although preclinical studies have been supportive, human trials of first-generation SP antagonists in multiple clinical settings have been disappointing.[80] Although it is assumed that research into these agents will advance over the coming years, currently there are no data available on their potential effectiveness in FMS.

Finally, in describing a "typical" neuroendocrine profile in FMS, one of the items we listed was low levels of IGF-1 or somatomedin-C.[108] In fact, this average profile is accounted for by a decreased level of IGF-1 in approximately one third of FMS patients.[289,290] IGF-1 is a factor produced in the liver, primarily in response to GH secretion. FMS patients may fail to produce GH under stimulatory conditions for a number of possible reasons including (A) low levels of GH-releasing hormone because of diminished NE tone[112]; (B) increased CRH levels, directly inhibiting somatomedin release[101]; and/or (C) decreased release of GH secondary to FMS-related sleep architecture disruption, as GH is primarily secreted during stage 3 and 4 non-REM sleep.[15,290]

Not for Reprint

Bennett et al[291] conducted a randomized placebo-controlled double-blind study of the clinical effects of GH therapy in 50 women with FMS and predetermined low IGF-1 levels. Patients were randomized to self-inject daily either GH or placebo (reconstituted excipient only) for 9 months. The dose of GH was adjusted to maintain blood IGF-1 levels at approximately 250 ng/mL. The GH-treated group achieved a significant improvement in FIQ scores and tender point counts at 9 months compared with baseline, whereas no significant improvement was observed in the placebo group. Patients' responses tended to lag behind the initiation of GH therapy by approximately 6 months, although measurable improvements in muscle strength and exercise performance were discernible after 3 months, with progressive improvement thereafter. Because GH is known to raise energy levels, increase exercise capacity, build muscle strength, and improve cognitive function in other patient groups with decreased basal GH levels,[292-295] the improvements seen in this trial may merely reflect the general metabolic effects of GH and not represent a syndrome-specific response. Moreover, although GH therapy would appear to offer this subgroup of patients some symptomatic improvement, financial considerations limit the viability of GH as a long-term therapy in this population.

Discussion

Because we are interested in drug development for FMS, our goal has been to formulate a model of FMS that is simple enough to serve as the basis for designing hypotheses and experiments for clinical research while taking into account the diversity of patients and the full spectrum of disease presentation. Our belief is that the field has advanced sufficiently to facilitate the identification and testing of compounds to treat the disorder. This view is based on an overview of both the scientific and clinical data available to date in FMS, as well as on a perspective developed by analogy with disorders that have already been established as clinical models, namely neuropathic pain and depression.

Although an understanding of the scientific basis for the disease remains in an early stage of development and the clinical evaluation of agents remains more empirical than proven, there are a number of common ideas that recur within the existing literature (summarized in Table 3). Beginning with a review of pain pathways and their role in both normal transmission of pain signals and the establishment of the maladaptive chronic pain state, one can identify many potential drug targets. Prioritizing the available options, the choices that emerge as the most probable to succeed are (A) facilitating the descending inhibitory pathways by increasing NE or 5-HT levels centrally; and/or (B) inhibition of central sensitization by blocking the effects of SP or Glu (via the NMDA receptor). Shifting to the available laboratory data on neurotransmitter measurements, the evidence suggests but does not confirm a role for 5-HT in the disorder. On the nociceptive side, the increased CSF levels of SP support the NK_1 receptor as a potential target. Likewise, the monoamines are prospective targets based on a review of the neuroendocrinology literature. Although the nature of CRH function in FMS remains controversial, there is agreement on the positive modulatory role that can assumed by 5-HT and/or NE on a chronic basis. In contrast, the interpretation of the physiological measurements of sleep function and neuroimaging do not tie as easily to identification of single agents. However, the well-established roles for 5-HT and GABA in maintaining sleep architecture support their consideration as potential drug targets.

Similarly, a review of the available clinical data supports some of the same approaches. Although there may be scientific merit in blocking excitatory neurotransmitters to treat chronic pain, there is insufficient empirical clinical evidence in other chronic pain states to predict efficacy of SP or NMDA blockers in FMS. Recent reports of positive results with atypical anticonvulsants, such as gabapentin and pregabalin, in the treatment of chronic pain conditions support consideration of this class for further testing. The bulk of the existing evidence, both in the literature and in clinical practice, however, points to the NE and 5-

TABLE 3

Evidence from Multiple Directions Converges on Similar Drug Targets

SUBJECT AREA REVIEWED	AGONIST (STIMULATORY) APPROACHES	ANTAGONIST (INHIBITORY) APPROACHES
Pain pathways	5-HT, NE (descending pathways)	SP Glutamate (NMDA)
Neurotransmitter changes	5-HT	SP
Neuroendocrinology of FMS	(CRH) 5-HT NE	(CRH)
Supportive clinical data in FMS	NE > 5-HT Atypical anticonvulsants (eg, pregabalin)	$5\text{-}HT_3$ Glutamate (NMDA)
Sleep changes	5-HT GABA	—

5-HT=serotonin; NE=norepinephrine; SP=substance P; NMDA=N-methyl-D-aspartate; FMS=fibromyalgia syndrome; CRH=corticotropin-releasing hormone; GABA=γ-aminobutyric acid.

Kranzler JD, Gendreau JF, Rao SG. *Psychopharmacology Bulletin.* Vol 36. No 1. 2002.

HT descending pathways as the most probable sites for successful intervention. In contrast to some of the laboratory results described earlier, currently the case is stronger for NE reuptake inhibition over 5-HT reuptake inhibition, based on clinical trials in neuropathic pain[185] as well as in FMS.[160,161] Both deserve further examination, however, and the combination may ultimately be preferred.

Therefore, we suggest, based on a review of the literature, that although many different targets for development of potential drugs exist, the most promising based on current knowledge are facilitation of NE and/or 5-HT transmission, use of atypical anticonvulsants, or blockade of SP. Modulation of monoamines has significant support both scientifically and clinically. The promise of atypical anticonvulsants is based on empirical clinical results. SP is the most speculative target because the evidence does not yet exist to either link definitively a disorder in SP to FMS or to demonstrate clinically that SP blockade can have an analgesic effect. In fact, SP antagonists have had a poor track record in the clinic to date, failing to demonstrate efficacy in a number of clinical pain paradigms.[80] We are swayed, however, by the hypothesis put forward by Hill,[80] who proposes that although blockade of SP may not be sufficient to treat most pain in and of itself, it may be useful for "reducing the behavioral response to a stressor such as inappropriate or intolerable sensory input." FMS, in our view, is the prototypical syndrome in which there is a "blurring of distinction between pain, emotion, and stress,"[80] and it may be ideally suited for treatment with NK_1 antagonists.

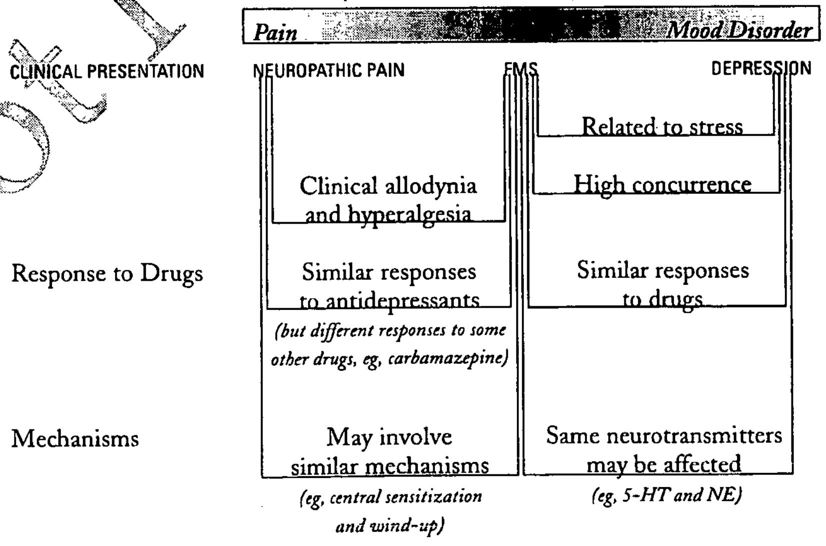
Based on the superior efficacy of the TCAs to the SSRIs in most reports, we are pursuing an SNRI approach. Venlafaxine is the only SNRI available on the US market, and it has demonstrated efficacy in FMS in a pilot study.[216] Two other SNRIs, duloxetine and milnacipran, will begin clinical trials for FMS shortly. Although all of these agents inhibit reuptake of both NE and 5-HT, they differ in relative activity: venlafaxine and duloxetine both favor inhibition of 5-HT reuptake while milnacipran favors inhibition of NE reuptake (Table 2).[147,180-183] The clinical relevance, if any, of this distinction remains to be determined.

Although there has been a tendency in the literature to fall into one of two camps, either portraying FMS as a chronic pain syndrome or as a somatic expression of psychological distress, we consider both views of the disorder to have merit and value in formulating potential therapeutic approaches (see Figure 4). In some aspects, FMS bears many similarities to human models of neuropathic pain, such as trigeminal neuralgia or diabetic neuropathy, in its response to many of the same drugs (such as TCAs and, perhaps, the newer anticonvulsants) and in the clinical expression of allodynia and hyperalgesia. However, there are certainly some stark differences between the clinical presentations, with widespread pain in FMS versus more localized pain in most neuropathic pain studies. Also, there are some differences in drug response; for instance, carbamazepine, which is first-line therapy for many types of neuropathic pain, has been reported to be of limited utility in FMS (DJ Clauw, MD, oral communication, August 20, 2000).

There are also many parallels to be drawn with the model of FMS as a somatic expression of a mood disorder such as depression. Most effective drugs in FMS are active in depression as well. There are striking similarities in the neuroendocrinology of FMS and of melancholic depression, as well as in the possible deficits in monoamine function that are proposed to underlie both disorders. Moreover, and perhaps most important, there is a high coincidence of FMS and depression, with a lifetime prevalence of more than 70% for those diagnosed with FMS.[296] Divergences from the depression model must also be borne in mind. Biologically, a deficiency of platelet 5-HT transporter has not been documented in the FMS cohorts studied to date, and they differ from depressed patients in their exaggerated ACTH response to CRH challenge. Also, although there has been minimal data collected examining the dose response of antidepressant drugs in FMS, doses that have been used in clinical trials to date have been on the lower end of what

FIGURE 4

FMS Has Elements of Neuropathic Pain and Depression


Pain
Mood Disorder
CLINICAL PRESENTATION
NEUROPATHIC PAIN
FMS
DEPRESSION
Related to stress
High concurrence
Clinical allodynia and hyperalgesia
Response to Drugs
Similar responses to antidepressants
(but different responses to some other drugs, eg, carbamazepine)
Similar responses to drugs
Mechanisms
May involve similar mechanisms
(eg, central sensitization and wind-up)
Same neurotransmitters may be affected
(eg, 5-HT and NE)

may be effective in depression, similar to the use of such drugs in chronic pain. Finally, at least in the primary care setting, the vast majority of FMS patients are not clinically depressed at the time of diagnosis, showing no variance in incidence of depression from the population at large.[34]

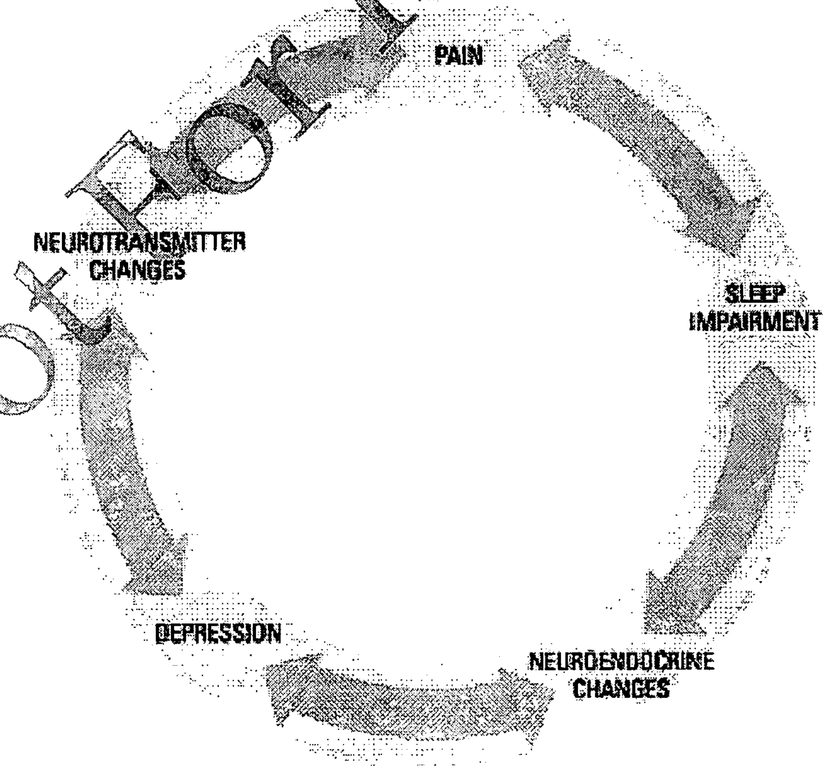
Rather than choosing one position or the other, we have incorporated both views into a conceptual disease model for FMS that, we believe, is consistent with both the available data and with our own experience. There is probably a spectrum of patients presenting with FMS symptoms, some with a "pure" chronic pain syndrome based on central sensitization; the high coincidence of other symptoms, such as sleep disturbance, fatigue, and mood disorder, supports the notion that FMS patients with pure chronic pain are the exception. In fact, the definition of FMS as a "syndrome" implies that, at least clinically, there is a constellation of symptoms making up the presentation that are difficult for the physician to pry apart in formulation, assessment, and plan. The basic and clinical data summarized previously provide a strong theoretical basis for a linkage among many of the findings that are observed clinically, leading us to the conceptual view of FMS outlined in Figure 5. We have limited our illustration and explanation to a few select clinical symptoms common in FMS patients, as well as a couple of biological observations. Expanding the number of items included, however, would not change the general paradigm that is portrayed.

The model considers the elements as interconnected, with no distinctions made or hierarchy presumed between the primary pathology and secondary symptoms. In fact, there is a reciprocal link between each and every item, with evidence for cause and effect available in both directions. For example, it is intuitively obvious that pain can interfere with sleep and that lack of restorative sleep can result in fatigue. Impaired sleep and chronic fatigue can be caused by, and also have been demonstrated to affect, neuroendocrine patterns, some of which may predispose to depression.[297,298] Depression, in turn, is associated with alterations in monoamine (or neuropeptide) function, which can impact the neural processing of pain. Conversely, depression may affect sleep architecture by way of its neurochemical and neuroendocrine repercussions or simply by way of the psychological distress that prevents restful sleep while depleting the person's sense of well being and energy level. Moldofsky and colleagues[135,136] have demonstrated that deprivation of late-stage sleep in and of itself can recreate the symptoms of FMS, completing the cycle in the other direction. It is probably not a coincidence that agents such as TCAs are effective in FMS because they have been demonstrated to independently affect each of the symptoms illustrated in Figure 5: they have antidepressant activity and are sedating and analgesic, increasing both 5-HT and NE levels and normalizing neuroendocrine circuits. Attempts to treat a single symptom within the complex, for example, with the use of hypnotics (eg, zolpidem) or analgesics (eg, NSAIDs), have generally been less successful.[173,258] Although perhaps oversimplifying the complex biology underlying the significant diversity across the FMS patient population, we have found this model useful in thinking about the design of new

FIGURE 5

A Model of Fibromyalgia as a Bidirectional Cycle

Many previous hypotheses of fibromyalgia (FMS) pathophysiology have assumed a hierarchical organization of FMS symptoms and findings; that is, pain precedes and is the cause of depression. In the model developed here, the various manifestations of FMS—including, but not limited to, pain, neurotransmitter changes, neuroendocrine changes, sleep changes, and fatigue—are all interconnected without a hierarchical arrangement. In fact, there is a reciprocal link between each and every factor, with evidence for cause and effect in both directions. As a result, any individual element has the potential, in the presence of a predisposing genetic background and/or environmental factors, to establish the cycle.



Kranzler JD, Gendreau JF, Rao SG. *Psychopharmacology Bulletin*. Vol 36. No 1. 2002.

therapeutic approaches, and we lean in the direction of selecting drug candidates and drug targets that may have impact on multiple pathways and across many related clinical symptoms.

Finally, we hope that this review will stimulate dialogue between the community of physicians who treat FMS patients and the scientific and clinical researchers well versed in the practice of studying brain physiology and pharmacology. Some of the ideas for future studies resulting from that dialogue will undoubtedly involve the use of pharmacologically active agents to further dissect the biology of FMS and/or to determine clinical response. We expect that, as a result of such collaborative efforts, our understanding of FMS, as well as of the physiological links between mind and body in the "functional somatic disorders" in general, will advance rapidly. ✤

Acknowledgments

The authors gratefully acknowledge the input, insight, and ideas that were generously shared by Drs. Larry Bradley, Randy Carpenter, Dan Clauw, Leslie Crofford, Mike Gendreau, Charles Nemeroff, Jon Russell, and Steven Stahl.

Funding/Support

This paper was fully supported by Cypress Bioscience, Inc., a publicly traded biotechnology company with a focus on development of products to treat fibromyalgia.

References

1. Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. *Arthritis Rheum.* 1995;38:19-28.
2. Wolfe F, Ross K, Anderson J, Russell IJ. Aspects of fibromyalgia in the general population: sex, pain threshold, and fibromyalgia symptoms. *J Rheumatol.* 1995;22:151-156.
3. Jacobsen S, Bredkjaer SR. The prevalence of fibromyalgia and widespread chronic musculoskeletal pain in the general population. *Scand J Rheumatol.* 1992;21:261-263.
4. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum.* 1990;33:160-172.
5. Aaron LA, Buchwald D. A review of the evidence for overlap among unexplained clinical conditions. *Ann Intern Med.* 2001;134(9 Pt 2):868-881.
6. Barsky AJ, Borus JF. Functional somatic syndromes. *Ann Intern Med.* 1999;130:910-921.
7. McCain GA. Fibromyalgia and myofascial pain. In: Wall PD, Melzack R, eds. *Textbook of Pain.* 3rd ed. Edinburgh, UK: Churchill Livingstone; 1994:475-493.
8. Hawley DJ, Wolfe F. Pain, disability, and pain/disability relationships in seven rheumatic disorders: a study of 1,522 patients. *J Rheumatol.* 1991;18:1552-1557.
9. White KP, Speechley M, Harth M, Ostbye T. Comparing self-reported function and work disability in 100 community cases of fibromyalgia syndrome versus controls in London, Ontario: the London Fibromyalgia Epidemiology Study. *Arthritis Rheum.* 1999;42:76-83.
10. Hadler NM. Fibromyalgia, chronic fatigue, and other iatrogenic diagnostic algorithms. Do some labels escalate illness in vulnerable patients? *Postgrad Med.* 1997;102:161-162, 165-166, 171-172 passim.
11. Hadler NM. Is fibromyalgia a useful diagnostic label? *Cleve Clin J Med.* 1996;63:85-87.
12. Wolfe F. For example is not evidence: fibromyalgia and the law. *J Rheumatol.* 2000;27:1115-1116.
13. Quintner JL, Cohen ML. Fibromyalgia falls foul of a fallacy. *Lancet.* 1999;353(9158):1092-1094.
14. Cohen ML, Quintner JL. Fibromyalgia syndrome, a problem of tautology. *Lancet.* 1993;342(8876):906-909.

15. Clauw DJ, Chrousos GP. Chronic pain and fatigue syndromes: overlapping clinical and neuroendocrine features and potential pathogenic mechanisms. *Neuroimmunomodulation.* 1997;4:134-153.
16. Yunus MB. Towards a model of pathophysiology of fibromyalgia: aberrant central pain mechanisms with peripheral modulation. *J Rheumatol.* 1992;19:846-850.
17. Bradley LA, McKendree-Smith NL, Alberts KR, Alarcon GS, Mountz JM, Deutsch G. Use of neuroimaging to understand abnormal pain sensitivity in fibromyalgia. *Curr Rheumatol Rep.* 2000;2:141-148.
18. Simms RW. Fibromyalgia is not a muscle disorder. *Am J Med Sci.* 1998;315:346-350.
19. Mountz JM, Bradley LA, Modell JG, et al. Fibromyalgia in women: abnormalities of regional cerebral blood flow in the thalamus and the caudate nucleus are associated with low pain threshold levels. *Arthritis Rheum.* 1995;38:926-938.
20. Arroyo JF, Cohen ML. Abnormal responses to electrocutaneous stimulation in fibromyalgia. *J Rheumatol.* 1993;20:1925-1931.
21. Sindrup SH, Jensen TS. Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. *Pain.* 1999;83:389-400.
22. Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. *Nature.* 1983;306:686-688.
23. Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. *Lancet.* 1999;353(9168):1959-1964.
24. *1998 National Ambulatory Medical Care Survey.* Princeton, NJ: Covance, Inc.; 1998.
25. Wolfe F, Anderson J, Harkness D, et al. Health status and disease severity in fibromyalgia: results of a six-center longitudinal study. *Arthritis Rheum.* 1997;40:1571-1579.
26. Martinez-Lavin M. Overlap of fibromyalgia with other medical conditions. *Curr Pain Headache Rep.* 2001;5:347-350.
27. White KP, Harth M. Classification, epidemiology, and natural history of fibromyalgia. *Curr Pain Headache Rep.* 2001;5:320-329.
28. Buskila D. Fibromyalgia, chronic fatigue syndrome, and myofascial pain syndrome. *Curr Opin Rheumatol.* 2001;13:117-127.
29. Boissevain MD, McCain GA. Toward an integrated understanding of fibromyalgia syndrome. II. Psychological and phenomenological aspects. *Pain.* 1991;45:239-248.
30. Boissevain MD, McCain GA. Toward an integrated understanding of fibromyalgia syndrome. I. Medical and pathophysiological aspects. *Pain.* 1991;45:227-238.
31. Hudson JI, Hudson MS, Pliner LF, Goldenberg DL, Pope HG Jr. Fibromyalgia and major affective disorder: a controlled phenomenology and family history study. *Am J Psychiatry.* 1985;142:441-446.
32. Bradley LA, Alberts KR. Psychological and behavioral approaches to pain management for patients with rheumatic disease. *Rheum Dis Clin North Am.* 1999;25:215-232,viii.
33. Singh BB, Berman BM, Hadhazy VA, Creamer P. A pilot study of cognitive behavioral therapy in fibromyalgia. *Altern Ther Health Med.* 1998;4:67-70.
34. Aaron LA, Bradley LA, Alarcon GS, et al. Psychiatric diagnoses in patients with fibromyalgia are related to health care-seeking behavior rather than to illness. *Arthritis Rheum.* 1996;39:436-445.
35. Aaron LA, Burke MM, Buchwald D. Overlapping conditions among patients with chronic fatigue syndrome, fibromyalgia, and temporomandibular disorder. *Arch Intern Med.* 2000;160:221-227.
36. Buchwald D, Garrity D. Comparison of patients with chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivities. *Arch Intern Med.* 1994;154:2049-2053.
37. Buchwald D. Fibromyalgia and chronic fatigue syndrome: similarities and differences. *Rheum Dis Clin North Am.* 1996;22:219-243.
38. Melzack R, Wall PD. Pain mechanisms: a new theory. *Science.* 1965;150:971-979.
39. Dickenson AH. Spinal cord pharmacology of pain. *Br J Anaesth.* 1995;75:193-200.
40. Jones SL, Gebhart GF. Spinal pathways mediating tonic, coeruleospinal, and raphe-spinal descending inhibition in the rat. *J Neurophysiol.* 1987;58:138-159.
41. DeLander GE, Hopkins CJ. Interdependence of spinal adenosinergic, serotonergic and noradrenergic systems mediating antinociception. *Neuropharmacology.* 1987;26:1791-1794.
42. Llewelyn MB, Azami J, Roberts MH. The effect of modification of 5-hydroxytryptamine function in nucleus raphe magnus on nociceptive threshold. *Brain Res.* 1984;306:165-170.
43. Fields HL, Heinricher MM, Mason P. Neurotransmitters in nociceptive modulatory circuits. *Annu Rev Neurosci.* 1991;14:219-245.
44. Coderre TJ, Katz J, Vaccarino AL, Melzack R. Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence. *Pain.* 1993;52:259-285.
45. Herrero JF, Laird JM, Lopez-Garcia JA. Wind-up of spinal cord neurons and pain sensation: much ado about something? *Prog Neurobiol.* 2000;61:169-203.
46. Eide PK. Wind-up and the NMDA receptor complex from a clinical perspective. *Eur J Pain.* 2000;4:5-15.
47. Davies SN, Lodge D. Evidence for involvement of N-methylaspartate receptors in 'wind-up' of class 2 neurons in the dorsal horn of the rat. *Brain Res.* 1987;424:402-406.
48. Dickenson AH, Sullivan AF. Electrophysiological studies on the effects of intrathecal morphine on nociceptive neurons in the rat dorsal horn. *Pain.* 1986;24:211-222.

49. Dickenson AH. A cure for wind up: NMDA receptor antagonists as potential analgesics. *Trends Pharmacol Sci.* 1990;11:307-309.
50. Dougherty PM, Palecek J, Paleckova V, Sorkin LS, Willis WD. The role of NMDA and non-NMDA excitatory amino acid receptors in the excitation of primate spinothalamic tract neurons by mechanical, chemical, thermal, and electrical stimuli. *J Neurosci.* 1992;12:3025-3041.
51. Dougherty PM, Willis WD. Enhancement of spinothalamic neuron responses to chemical and mechanical stimuli following combined micro-iontophoretic application of N-methyl-D-aspartic acid and substance P. *Pain.* 1991;47:85-93.
52. Dougherty PM, Palecek J, Zorn S, Willis WD. Combined application of excitatory amino acids and substance P produces long-lasting changes in responses of primate spinothalamic tract neurons. *Brain Res Brain Res Rev.* 1993;18:227-246.
53. Urban MO, Gebhart GF. Supraspinal contributions to hyperalgesia. *Proc Natl Acad Sci USA.* 1999;96:7687-7692.
54. Kovelowski CJ, OssipovMH, Sun H, Lai J, Malan TP, Porreca F. Supraspinal cholecystokinin may drive tonic descending facilitation mechanisms to maintain neuropathic pain in the rat. *Pain.* 2000;87:265-273.
55. Coutinho SV, Urban MO, Gebhart GF. Role of glutamate receptors and nitric oxide in the rostral ventromedial medulla in visceral hyperalgesia. *Pain.* 1998;78:59-69.
56. Urban MO, Coutinho SV, Gebhart GF. Involvement of excitatory amino acid receptors and nitric oxide in the rostral ventromedial medulla in modulating secondary hyperalgesia produced by mustard oil. *Pain.* 1999;81:45-55.
57. Urban MO, Gebhart GF. The glutamate synapse: a target in the pharmacological management of hyperalgesic pain states. *Prog Brain Res.* 1998;116:407-420.
58. Bennett GJ, Xie YK. A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. *Pain.* 1988;33:87-107.
59. Mogil JS, Grisel JE. Transgenic studies of pain. *Pain.* 1998;77:107-128.
60. Russell IJ. Advances in fibromyalgia: possible role for central neurochemicals. *Am J Med Sci.* 1998;315:377-384.
61. Russell IJ, Vaeroy H, Javors M, Nyberg F. Cerebrospinal fluid biogenic amine metabolites in fibromyalgia/fibrositis syndrome and rheumatoid arthritis. *Arthritis Rheum.* 1992;35:550-556.
62. Russell IJ, Orr MD, Littman B, et al. Elevated cerebrospinal fluid levels of substance P in patients with the fibromyalgia syndrome. *Arthritis Rheum.* 1994;37:1593-1601.
63. Moldofsky H. Sleep and musculoskeletal pain. *Am J Med.* 1986;81(3A):85-89.
64. Alnigenis MN, Barland P. Fibromyalgia syndrome and serotonin. *Clin Exp Rheumatol.* 2001;19:205-210.
65. Fuller RW. The involvement of serotonin in regulation of pituitary-adrenocortical function. *Front Neuroendocrinol.* 1992;13:250-270.
66. Moldofsky H. Rheumatic pain modulation syndrome: the interrelationships between sleep, central nervous system serotonin, and pain. *Adv Neurol.* 1982;33:51-57.
67. Houvenagel E, Forzy G, Leloire O, et al. Cerebrospinal fluid monoamines in primary fibromyalgia. *Rev Rhum Mal Osteoartic.* 1990;57:21-23.
68. Legangneux E, Mora JJ, Spreux-Varoquaux O, et al. Cerebrospinal fluid biogenic amine metabolites, plasma-rich platelet serotonin and [3H]imipramine reuptake in the primary fibromyalgia syndrome. *Rheumatology (Oxf).* 2001;40:290-296.
69. Hrycaj P, Stratz T, Muller W. Platelet 3H-imipramine uptake receptor density and serum serotonin levels in patients with fibromyalgia/fibrositis syndrome. *J Rheumatol.* 1993;20:1986-1988.
70. Ernberg M, Voog U, Alstergren P, Lundeberg T, Kopp S. Plasma and serum serotonin levels and their relationship to orofacial pain and anxiety in fibromyalgia. *J Orofac Pain.* 2000;14:37-46.
71. Mann JJ. Role of the serotonergic system in the pathogenesis of major depression and suicidal behavior. *Neuropsychopharmacology.* 1999;21(2 suppl):99S-105S.
72. Martensson B, Nyberg S, Toresson G, Brodin E, Bertilsson L. Fluoxetine treatment of depression: clinical effects, drug concentrations and monoamine metabolites and N-terminally extended substance P in cerebrospinal fluid. *Acta Psychiatr Scand.* 1989;79:586-596.
73. Gibbons RD, Davis JM. Consistent evidence for a biological subtype of depression characterized by low CSF monoamine levels. *Acta Psychiatr Scand.* 1986;74:8-12.
74. Stahl SM, Woo DJ, Mefford IN, Berger PA, Ciaranello RD. Hyperserotonemia and platelet serotonin uptake and release in schizophrenia and affective disorders. *Am J Psychiatry.* 1983;140:26-30.
75. Owens MJ, Nemeroff CB. Role of serotonin in the pathophysiology of depression: focus on the serotonin transporter. *Clin Chem.* 1994;40:288-295.
76. Russell IJ, Michalek JE, Vipraio GA, Fletcher EM, Javors MA, Bowden CA. Platelet 3H-imipramine uptake receptor density and serum serotonin levels in patients with fibromyalgia/fibrositis syndrome. *J Rheumatol.* 1992;19:104-109.
77. Magni G, Andreoli F, Arduino C, et al. [3H] imipramine binding sites are decreased in platelets of chronic pain patients. *Acta Psychiatr Scand.* 1987;75:108-110.

78. Kravitz HM, Katz R, Kot E, Helmke N, Fawcett J. Biochemical clues to a fibromyalgia-depression link: imipramine binding in patients with fibromyalgia or depression and in healthy controls. *J Rheumatol.* 1992;19:1428-1432.
79. Offenbaecher M, Bondy B, de Jonge S, et al. Possible association of fibromyalgia with a polymorphism in the serotonin transporter gene regulatory region. *Arthritis Rheum.* 1999;42:2482-2488.
80. Hill R. NK1 (substance P) receptor antagonists: why are they not analgesic in humans? *Trends Pharmacol Sci.* 2000;21:244-246.
81. Hokfelt T, Pernow B, Wahren J. Substance P: a pioneer amongst neuropeptides. *J Intern Med.* 2001;249:27-40.
82. Dougherty PM, Palecek J, Paleckova V, Willis WD. Infusion of substance P or neurokinin A by microdialysis alters responses of primate spinothalamic tract neurons to cutaneous stimuli and to iontophoretically released excitatory amino acids. *Pain.* 1995;61:411-425.
83. Vaeroy H, Helle R, Forre O, Kass E, Terenius L. Elevated CSF levels of substance P and high incidence of Raynaud phenomenon in patients with fibromyalgia: new features for diagnosis. *Pain.* 1988;32:21-26.
84. Welin M, Bragee B, Nyberg F, Kristiansson M. Elevated substance P levels are contrasted by a decrease in met-enkephalin-arg-phe levels in csf from fibromyalgia patients. *J Musculoskeletal Pain.* 1995;3(suppl 1):4.
85. Bradley LA, Alberts KR, Alarcon GS, Alexander MR. Abnormal brain regional cerebral blood flow (rCBF) and cerebrospinal fluid (CSF) levels of substance P (SP) in patients and non-patients with fibromyalgia (FM). *Arthritis Rheum.* 1996;39(suppl 9):S212.
86. Hornfeldt CS, Sun X, Larson AA. The NH2-terminus of substance P modulates NMDA-induced activity in the mouse spinal cord. *J Neurosci.* 1994;14(5 Pt 2):3364-3369.
87. Oku R, Satoh M, Takagi H. Release of substance P from the spinal dorsal horn is enhanced in polyarthritic rats. *Neurosci Lett.* 1987;74:315-319.
88. Schaible HG, Jarrott B, Hope PJ, Duggan AW. Release of immunoreactive substance P in the spinal cord during development of acute arthritis in the knee joint of the cat: a study with antibody microprobes. *Brain Res.* 1990;529:214-223.
89. Duggan AW, Hendry IA, Morton CR, Hutchison WD, Zhao ZQ. Cutaneous stimuli releasing immunoreactive substance P in the dorsal horn of the cat. *Brain Res.* 1988;451:261-273.
90. Otsuka M, Yoshioka K. Neurotransmitter functions of mammalian tachykinins. *Physiol Rev.* 1993;73:229-308.
91. Walker PD, Riley LA, Hart RP, Jonakait GM. Serotonin regulation of tachykinin biosynthesis in the rat neostriatum. *Brain Res.* 1991;546:33-39.
92. Murphy RM, Zemlan FP. Differential effects of substance P on serotonin-modulated spinal nociceptive reflexes. *Psychopharmacology (Berl).* 1987;93:118-121.
93. Sharma HS, Nyberg F, Olsson Y, Dey PK. Alteration of substance P after trauma to the spinal cord: an experimental study in the rat. *Neuroscience.* 1990;38:205-212.
94. Strittmatter M, Grauer M, Isenberg E, et al. Cerebrospinal fluid neuropeptides and monoaminergic transmitters in patients with trigeminal neuralgia. *Headache.* 1997;37:211-216.
95. Sjostrom S, Tamsen A, Hartvig P, Folkesson R, Terenius L. Cerebrospinal fluid concentrations of substance P and (met)enkephalin-Arg6-Phe7 during surgery and patient-controlled analgesia. *Anesth Analg.* 1988;67:976-981.
96. Tsigos C, Diemel LT, White A, Tomlinson DR, Young RJ. Cerebrospinal fluid levels of substance P and calcitonin-gene-related peptide: correlation with sural nerve levels and neuropathic signs in sensory diabetic polyneuropathy. *Clin Sci (Lond).* 1993;84:305-311.
97. Fischer HP, Eich W, Russell IJ. A possible role for saliva as a diagnostic fluid in patients with chronic pain. *Semin Arthritis Rheum.* 1998;27:348-359.
98. Schwarz MJ, Spath M, Muller-Bardorff H, Pongratz DE, Bondy B, Ackenheil M. Relationship of substance P, 5-hydroxyindole acetic acid and tryptophan in serum of fibromyalgia patients. *Neurosci Lett.* 1999;259:196-198.
99. Chrousos GP. Stressors, stress, and neuroendocrine integration of the adaptive response. The 1997 Hans Selye Memorial Lecture. *Ann N Y Acad Sci.* 1998;851:311-335.
100. Heim C, Nemeroff CB. The impact of early adverse experiences on brain systems involved in the pathophysiology of anxiety and affective disorders. *Biol Psychiatry.* 1999;46:1509-1522.
101. Neeck G, Crofford LJ. Neuroendocrine perturbations in fibromyalgia and chronic fatigue syndrome. *Rheum Dis Clin North Am.* 2000;26:989-1002.
102. Peterfreund RA, Vale WW. Ovine corticotropin-releasing factor stimulates somatostatin secretion from cultured brain cells. *Endocrinology.* 1983;112:1275-1278.
103. Frias J, Puertas A, Ruiz E, Ortega E. Effect of corticotropin releasing factor (CRF) injected into the median eminence on LH secretion in male rats. *Neurochem Res.* 1997;22:171-174.
104. McCain GA, Tilbe KS. Diurnal hormone variation in fibromyalgia syndrome: a comparison with rheumatoid arthritis. *J Rheumatol Suppl.* 1989;19:154-157.
105. Crofford LJ, Pillemer SR, Kalogeras KT, et al. Hypothalamic-pituitary-adrenal axis perturbations in patients with fibromyalgia. *Arthritis Rheum.* 1994;37:1583-1592.

106. Griep EN, Boersma JW, de Kloet ER. Altered reactivity of the hypothalamic-pituitary-adrenal axis in the primary fibromyalgia syndrome. *J Rheumatol.* 1993;20:469-474.
107. Riedel W, Layka H, Neeck G. Secretory pattern of GH, TSH, thyroid hormones, ACTH, cortisol, FSH, and LH in patients with fibromyalgia syndrome following systemic injection of the relevant hypothalamic-releasing hormones. *Z Rheumatol.* 1998;57(suppl 2):81-87.
108. Bennett RM, Cook DM, Clark SR, Burckhardt CS, Campbell SM. Hypothalamic-pituitary-insulin-like growth factor-I axis dysfunction in patients with fibromyalgia. *J Rheumatol.* 1997;24:1384-1389.
109. Neeck G, Riedel W. Thyroid function in patients with fibromyalgia syndrome. *J Rheumatol.* 1992;19:1120-1122.
110. Cohen H, Neumann L, Shore M, Amir M, Cassuto Y, Buskila D. Autonomic dysfunction in patients with fibromyalgia: application of power spectral analysis of heart rate variability. *Semin Arthritis Rheum.* 2000;29:217-227.
111. Kasckow JW, Baker D, Geracioti TD Jr. Corticotropin-releasing hormone in depression and post-traumatic stress disorder. *Peptides.* 2001;22:845-851.
112. Torpy DJ, Papanicolaou DA, Lotsikas AJ, Wilder RL, Chrousos GP, Pillemer SR. Responses of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis to interleukin-6: a pilot study in fibromyalgia. *Arthritis Rheum.* 2000;43:872-880.
113. Heim C, Ehlert U, Hellhammer DH. The potential role of hypocortisolism in the pathophysiology of stress-related bodily disorders. *Psychoneuroendocrinology.* 2000;25:1-35.
114. Swanson LW, Sawchenko PE, Rivier J, Vale WW. Organization of ovine corticotropin-releasing factor immunoreactive cells and fibers in the rat brain: an immunohistochemical study. *Neuroendocrinology.* 1983;36:165-186.
115. Nemeroff CB, Widerlov E, Bissette G, et al. Elevated concentrations of CSF corticotropin releasing factor-like immunoreactivity in depressed patients. *Science.* 1984;226:1342-1344.
116. Gold PW, Chrousos GP. The endocrinology of melancholic and atypical depression: relation to neurocircuitry and somatic consequences. *Proc Assoc Am Physicians.* 1999;111:22-34.
117. Jessop DS, Renshaw D, Larsen PJ, Chowdrey HS, Harbuz MS. Substance P is involved in terminating the hypothalamo-pituitary-adrenal axis response to acute stress through centrally located neurokinin-1 receptors. *Stress.* 2000;3:209-220.
118. Torpy DJ, Grice JE, Hockings GI, Crosbie GV, Walters MM, Jackson RV. The effect of desipramine on basal and naloxone-stimulated cortisol secretion in humans: interaction of two drugs acting on noradrenergic control of adrenocorticotropin secretion. *J Clin Endocrinol Metab.* 1995;80:802-806.
119. Holsboer F. The rationale for corticotropin-releasing hormone receptor (CRH-R) antagonists to treat depression and anxiety. *J Psychiatr Res.* 1999;33:181-214.
120. Smythe HA, Moldofsky H. Two contributions to understanding of the "fibrositis" syndrome. *Bull Rheum Dis.* 1977;28:928-931.
121. Yunus M, Masi AT, Calabro JJ, Miller KA, Feigenbaum SL. Primary fibromyalgia (fibrositis): clinical study of 50 patients with matched normal controls. *Semin Arthritis Rheum.* 1981;11:151-171.
122. Roizenblatt S, Moldofsky H, Benedito-Silva AA, Tufik S. Alpha sleep characteristics in fibromyalgia. *Arthritis Rheum.* 2001;44:222-230.
123. Sergi M, Rizzi M, Braghiroli A, et al. Periodic breathing during sleep in patients affected by fibromyalgia syndrome. *Eur Respir J.* 1999;14:203-208.
124. Wittig RM, Zorick FJ, Blumer D, Heilbronn M, Roth T. Disturbed sleep in patients complaining of chronic pain. *J Nerv Ment Dis.* 1982;170:429-431.
125. Horne JA, Shackell BS. Alpha-like EEG activity in non-REM sleep and the fibromyalgia (fibrositis) syndrome. *Electroencephalogr Clin Neurophysiol.* 1991;79:271-276.
126. Branco J, Atalaia A, Paiva T. Sleep cycles and alpha-delta sleep in fibromyalgia syndrome. *J Rheumatol.* 1994;21:1113-1117.
127. Drewes AM, Nielsen KD, Taagholt SJ, Bjerregard K, Svendsen L, Gade J. Sleep intensity in fibromyalgia: focus on the microstructure of the sleep process. *Br J Rheumatol.* 1995;34:629-635.
128. Drewes AM, Gade K, Nielsen KD, Bjerregard K, Taagholt SJ, Svendsen L. Clustering of sleep electroencephalographic patterns in patients with the fibromyalgia syndrome. *Br J Rheumatol.* 1995;34:1151-1156.
129. Perlis ML, Giles DE, Bootzin RR, et al. Alpha sleep and information processing, perception of sleep, pain, and arousability in fibromyalgia. *Int J Neurosci.* 1997;89:265-280.
130. Dauvilliers Y, Touchon J. Sleep in fibromyalgia: review of clinical and polysomnographic data (in French). *Neurophysiol Clin.* 2001;31:18-33.
131. Tayag-Kier CE, Keenan GF, Scalzi LV, et al. Sleep and periodic limb movement in sleep in juvenile fibromyalgia. *Pediatrics.* 2000;106:E70.
132. Schneider-Helmert D, Whitehouse I, Kumar A, Lijzenga C. Insomnia and alpha sleep in chronic non-organic pain as compared to primary insomnia. *Neuropsychobiology.* 2001;43:54-58.
133. Gursky JT, Krahn LE. The effects of antidepressants on sleep: a review *Harv Rev Psychiatry.* 2000;8:298-306.

134. Lentz MJ, Landis CA, Rothermel J, Shaver JL. Effects of selective slow wave sleep disruption on musculoskeletal pain and fatigue in middle-aged women. *J Rheumatol.* 1999;26:1586-1592.
135. Moldofsky H, Scarisbrick P, England R, Smythe H. Musculosketal symptoms and non-REM sleep disturbance in patients with "fibrositis syndrome" and healthy subjects. *Psychosom Med.* 1975;37:341-351.
136. Moldofsky H, Scarisbrick P. Induction of neurasthenic musculoskeletal pain syndrome by selective sleep stage deprivation. *Psychosom Med.* 1976;38:35-44.
137. Moldofsky H. Fibromyalgia, sleep disorder and chronic fatigue syndrome. *Ciba Found Symp.* 1993;173:262-271.
138. Pillemer SR, Bradley LA, Crofford LJ, Moldofsky H, Chrousos GP. The neuroscience and endocrinology of fibromyalgia. *Arthritis Rheum.* 1997;40:1928-1939.
139. Scharf MB, Hauck M, Stover R, McDannold M, Berkowitz D. Effect of gamma-hydroxybutyrate on pain, fatigue, and the alpha sleep anomaly in patients with fibromyalgia. Preliminary report. *J Rheumatol.* 1998;25:1986-1990.
140. Carette S, Oakson G, Guimont C, Steriade M. Sleep electroencephalography and the clinical response to amitriptyline in patients with fibromyalgia. *Arthritis Rheum.* 1995;38:1211-1217.
141. Kwiatek R, Barnden L, Tedman R, et al. Regional cerebral blood flow in fibromyalgia: single-photon-emission computed tomography evidence of reduction in the pontine tegmentum and thalami. *Arthritis Rheum.* 2000;43:2823-2833.
142. Johansson G, Risberg J, Rosenhall U, Orndahl G, Svennerholm L, Nystrom S. Cerebral dysfunction in fibromyalgia: evidence from regional cerebral blood flow measurements, otoneurological tests and cerebrospinal fluid analysis. *Acta Psychiatr Scand.* 1995;91:86-94.
143. Lekander M, Fredrikson M, Wik G. Neuroimmune relations in patients with fibromyalgia: a positron emission tomography study. *Neurosci Lett.* 2000;282:193-196.
144. Petzke F, Gracely RH, Wolf JM, Clauw DJ. Pressure pain in fibromyalgia and healthy controls: functional MRI subjective pain experience versus objective stimulus intensity. *Arthritis Rheum.* 2000;43:9S.
145. Alavi A, Hirsch LJ. Studies of central nervous system disorders with single photon emission computed tomography and positron emission tomography: evolution over the past 2 decades. *Semin Nucl Med.* 1991;21:58-81.
146. Detre JA, Floyd TF. Functional MRI and its applications to the clinical neurosciences. *Neuroscientist.* 2001;7:64-79.
147. Sanchez C, Hyttel J. Comparison of the effects of antidepressants and their metabolites on reuptake of biogenic amines and on receptor binding. *Cell Mol Neurobiol.* 1999;19:467-489.
148. San Pedro EC, Mountz JM, Mountz JD, Liu HG, Katholi CR, Deutsch G. Familial painful restless legs syndrome correlates with pain dependent variation of blood flow to the caudate, thalamus, and anterior cingulate gyrus. *J Rheumatol.* 1998;25:2270-2275.
149. Hsieh JC, Belfrage M, Stone-Elander S, Hansson P, Ingvar M. Central representation of chronic ongoing neuropathic pain studied by positron emission tomography. *Pain.* 1995;63:225-236.
150. Di Piero V, Jones AK, Iannotti F, et al. Chronic pain: a PET study of the central effects of percutaneous high cervical cordotomy. *Pain.* 1991;46:9-12.
151. Iadarola MJ, Max MB, Berman KF, et al. Unilateral decrease in thalamic activity observed with positron emission tomography in patients with chronic neuropathic pain. *Pain.* 1995;63:55-64.
152. Soares JC, Mann JJ. The functional neuroanatomy of mood disorders. *J Psychiatr Res.* 1997;31:393-432.
153. Reiman EM. The application of positron emission tomography to the study of normal and pathologic emotions. *J Clin Psychiatry.* 1997;58(suppl 6):4-12.
154. Gracely RH, Kwilosz DM. The Descriptor Differential Scale: applying psychophysical principles to clinical pain assessment. *Pain.* 1988;35:279-288.
155. Felson DT, Anderson JJ, Boers M, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. *Arthritis Rheum.* 1993;36:729-740.
156. Felson DT. Choosing a core set of disease activity measures for rheumatoid arthritis clinical trials. *J Rheumatol.* 1993;20:531-534.
157. Burckhardt CS, Clark SR, Bennett RM. The fibromyalgia impact questionnaire: development and validation. *J Rheumatol.* 1991;18:728-733.
158. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. *Pain.* 1975;1:277-299.
159. Melzack R. The short-form McGill Pain Questionnaire. *Pain.* 1987;30:191-197.
160. Arnold LM, Keck PE Jr, Welge JA. Antidepressant treatment of fibromyalgia. A meta-analysis and review. *Psychosomatics.* 2000;41:104-113.
161. O'Malley PG, Balden E, Tomkins G, Santoro J, Kroenke K, Jackson JL. Treatment of fibromyalgia with antidepressants: a meta-analysis. *J Gen Intern Med.* 2000;15:659-666.
162. Wolfe F. Fibromyalgia. *Rheum Dis Clin North Am.* 1990;16:681-698.
163. Burckhardt CS, O'Reilly CA, Wiens AN, Clark SR, Campbell SM, Bennett RM. Assessing depression in fibromyalgia patients. *Arthritis Care Res.* 1994;7:35-39.

164. Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol.* 1967;6:278-296.
165. Hamilton M. Rating depressive patients. *J Clin Psychiatry.* 1980;41(12 Pt 2):21-24.
166. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry.* 1979;134:382-389.
167. Beck AT, Ward CH, Mendelson M. An inventory for measuring depression. *Arch Gen Psychiatry.* 1961;4:561-571.
168. Buskila D. Drug therapy. *Baillieres Best Pract Res Clin Rheumatol.* 1999;13:479-485.
169. Leventhal LJ. Management of fibromyalgia. *Ann Intern Med.* 1999;131:850-858.
170. Lautenschlager J. Present state of medication therapy in fibromyalgia syndrome. *Scand J Rheumatol Suppl.* 2000;113:32-36.
171. Bennett RM. Pharmacological treatment of fibromyalgia. *J Functional Syndromes.* 2001;1:79-92.
172. Wolfe F, Anderson J, Harkness D, et al. A prospective, longitudinal, multicenter study of service utilization and costs in fibromyalgia. *Arthritis Rheum.* 1997;40:1560-1570.
173. Goldenberg DL, Felson DT, Dinerman H. A randomized, controlled trial of amitriptyline and naproxen in the treatment of patients with fibromyalgia. *Arthritis Rheum.* 1986;29:1371-1377.
174. Yunus MB, Masi AT, Aldag JC. Short term effects of ibuprofen in primary fibromyalgia syndrome: a double blind, placebo controlled trial. *J Rheumatol.* 1989;16:527-532.
175. Wolfe F, Zhao S, Lane N. Preference for nonsteroidal antiinflammatory drugs over acetaminophen by rheumatic disease patients: a survey of 1,799 patients with osteoarthritis, rheumatoid arthritis, and fibromyalgia. *Arthritis Rheum.* 2000;43:378-385.
176. Russell IJ, Fletcher EM, Michalek JE, McBroom PC, Hester GG. Treatment of primary fibrositis/fibromyalgia syndrome with ibuprofen and alprazolam. A double-blind, placebo-controlled study. *Arthritis Rheum.* 1991;34:552-560.
177. Quijada-Carrera J, Valenzuela-Castano A, Povedano-Gomez J, et al. Comparison of tenoxicam and bromazepan in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled trial. *Pain.* 1996;65:221-225.
178. Gronblad M, Nykanen J, Konttinen Y, Jarvinen E, Helve T. Effect of zopiclone on sleep quality, morning stiffness, widespread tenderness and pain and general discomfort in primary fibromyalgia patients. A double-blind randomized trial. *Clin Rheumatol.* 1993;12:186-191.
179. Drewes AM, Andreasen A, Jennum P, Nielsen KD. Zopiclone in the treatment of sleep abnormalities in fibromyalgia. *Scand J Rheumatol.* 1991;20:288-293.
180. Moret C, Charveron M, Finberg JP, Couzinier JP, Briley M. Biochemical profile of midalcipran (F 2207), 1-phenyl-1-diethyl-aminocarbonyl-2-aminomethyl-cyclopropane (Z) hydrochloride, a potential fourth generation antidepressant drug. *Neuropharmacology.* 1985;24:1211-1219.
181. Palmier C, Puozzo C, Lenehan T, Briley M. Monoamine uptake inhibition by plasma from healthy volunteers after single oral doses of the antidepressant milnacipran. *Eur J Clin Pharmacol.* 1989;37:235-238.
182. Kasamo K, Blier P, De Montigny C. Blockade of the serotonin and norepinephrine uptake processes by duloxetine: in vitro and in vivo studies in the rat brain. *J Pharmacol Exp Ther.* 1996;277:278-286.
183. Bymaster FP, Hemrick-Luecke SR, Threlkeld PG, et al. Affinity of duloxetine and venlafaxine for 5HT and norepinephrine transporters. NR 534. Poster presented at: 154th Annual Meeting of the American Psychiatric Association; May 9, 2001; New Orleans, LA.
184. Fishbain D. Evidence-based data on pain relief with antidepressants. *Ann Med.* 2000;32:305-316.
185. Atkinson JH, Slater MA, Wahlgren DR, et al. Effects of noradrenergic and serotonergic antidepressants on chronic low back pain intensity. *Pain.* 1999;83:137-145.
186. Kobayashi H, Hasegawa Y, Ono H. Cyclobenzaprine, a centrally acting muscle relaxant, acts on descending serotonergic systems. *Eur J Pharmacol.* 1996;311:29-35.
187. Eisenach JC, Gebhart GF. Intrathecal amitriptyline acts as an N-methyl-D-aspartate receptor antagonist in the presence of inflammatory hyperalgesia in rats. *Anesthesiology.* 1995;83:1046-1054.
188. Reynolds IJ, Miller RJ. Tricyclic antidepressants block N-methyl-D-aspartate receptors: similarities to the action of zinc. *Br J Pharmacol.* 1988;95:95-102.
189. McCaslin PP, Yu XZ, Ho IK, Smith TG. Amitriptyline prevents N-methyl-D-aspartate (NMDA)-induced toxicity, does not prevent NMDA-induced elevations of extracellular glutamate, but augments kainate-induced elevations of glutamate. *J Neurochem.* 1992;59:401-405.
190. Cai Z, McCaslin PP. Amitriptyline, desipramine, cyproheptadine and carbamazepine, in concentrations used therapeutically, reduce kainate- and N-methyl-D-aspartate-induced intracellular Ca2+ levels in neuronal culture. *Eur J Pharmacol.* 1992;219:53-57.
191. Watanabe Y, Saito H, Abe K. Tricyclic antidepressants block NMDA receptor-mediated synaptic responses and induction of long-term potentiation in rat hippocampal slices. *Neuropharmacology.* 1993;32:479-486.
192. Kuo CC. Imipramine inhibition of transient K+ current: an external open channel blocker preventing fast inactivation. *Biophys J.* 1998;75:2845-2857.

193. Nakazawa K, Inoue K, Ohno Y. Block and unblock by imipramine of cloned and mutated P2X2 receptor/channel expressed in Xenopus oocytes. *Neurosci Lett.* 1999;264:93-96.
194. Park TJ, Shin SY, Suh BC, et al. Differential inhibition of catecholamine secretion by amitriptyline through blockage of nicotinic receptors, sodium channels, and calcium channels in bovine adrenal chromaffin cells. *Synapse.* 1998;29:248-256.
195. Kent JM. SNaRIs, NaSSAs, and NaRIs: new agents for the treatment of depression. *Lancet.* 2000;355(9207):911-918.
196. Max MB, Lynch SA, Muir J, Shoaf SE, Smoller B, Dubner R. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. *N Engl J Med.* 1992;326:1250-1256.
197. Max MB, Schafer SC, Culnane M, Smoller B, Dubner R, Gracely RH. Amitriptyline, but not lorazepam, relieves postherpetic neuralgia. *Neurology.* 1988;38:1427-1432.
198. Watson CP, Evans RJ, Reed K, Merskey H, Goldsmith L, Warsh J. Amitriptyline versus placebo in postherpetic neuralgia. *Neurology.* 1982;32:671-673.
199. Watson CP, Chipman M, Reed K, Evans RJ, Birkett N. Amitriptyline versus maprotiline in postherpetic neuralgia: a randomized, double-blind, crossover trial. *Pain.* 1992;48:29-36.
200. Celiker R, Cagavi Z. Comparison of amitriptyline and sertraline in the treatment of fibromyalgia syndrome. Poster presented at: 20th Annual Scientific Meeting of the American Pain Society; April 20, 2001; Phoenix, AZ.
201. Goldenberg D, Mayskiy M, Mossey C, Ruthazer R, Schmid C. A randomized, double-blind crossover trial of fluoxetine and amitriptyline in the treatment of fibromyalgia. *Arthritis Rheum.* 1996;39:1852-1859.
202. Hannonen P, Malminiemi K, Yli-Kerttula U, Isomeri R, Roponen P. A randomized, double-blind, placebo-controlled study of moclobemide and amitriptyline in the treatment of fibromyalgia in females without psychiatric disorder. *Br J Rheumatol.* 1998;37:1279-1286.
203. Smith AJ. The analgesic effects of selective serotonin reuptake inhibitors. *J Psychopharmacol.* 1998;12:407-413.
204. Wolfe F, Cathey MA, Hawley DJ. A double-blind placebo controlled trial of fluoxetine in fibromyalgia. *Scand J Rheumatol.* 1994;23:255-259.
205. Nutt DJ, Forshall S, Bell C, et al. Mechanisms of action of selective serotonin reuptake inhibitors in the treatment of psychiatric disorders. *Eur Neuropsychopharmacol.* 1999;9(suppl 3):S81-S86.
206. Brunello N, den Boer JA, Judd LL, et al. Social phobia: diagnosis and epidemiology, neurobiology and pharmacology, comorbidity and treatment. *J Affect Disord.* 2000;60:61-74.
207. Norregaard J, Volkmann H, Danneskiold-Samsoe B. A randomized controlled trial of citalopram in the treatment of fibromyalgia. *Pain.* 1995;61:445-459.
208. Anderberg UM, Marteinsdottir I, von Knorring L. Citalopram in patients with fibromyalgia: a randomized, double-blind, placebo-controlled study. *Eur J Pain.* 2000;4:27-35.
209. Ansari A. The efficacy of newer antidepressants in the treatment of chronic pain: a review of current literature. *Harv Rev Psychiatry.* 2000;7:257-277.
210. Jung AC, Staiger T, Sullivan M. The efficacy of selective serotonin reuptake inhibitors for the management of chronic pain. *J Gen Intern Med.* 1997;12:384-389.
211. Adly C, Straumanis J, Chesson A. Fluoxetine prophylaxis of migraine. *Headache.* 1992;32:101-104.
212. Saper JR, Silberstein SD, Lake AE 3rd, Winters ME. Fluoxetine and migraine: comparison of double-blind trials. *Headache.* 1995;35:233.
213. Ressler KJ, Nemeroff CB. Role of norepinephrine in the pathophysiology and treatment of mood disorders. *Biol Psychiatry.* 1999;46:1219-1233.
214. Pitsikas N. Duloxetine Eli Lilly & Co. *Curr Opin Investig Drugs.* 2000;1:116-121.
215. Turcotte JE, Debonnel G, de Montigny C, Hebert C, Blier P. Assessment of the serotonin and norepinephrine reuptake blocking properties of duloxetine in healthy subjects. *Neuropsychopharmacology.* 2001;24:511-521.
216. Dwight MM, Arnold LM, O'Brien H, Metzger R, Morris-Park E, Keck PE Jr. An open clinical trial of venlafaxine treatment of fibromyalgia. *Psychosomatics.* 1998;39:14-17.
217. Harvey AT, Rudolph RL, Preskorn SH. Evidence of the dual mechanisms of action of venlafaxine. *Arch Gen Psychiatry.* 2000;57:503-509.
218. Roseboom PH, Kalin NH. Neuropharmacology of venlafaxine. *Depress Anxiety.* 2000;12(suppl 1):20-29.
219. Galli A, DeFelice LJ, Duke BJ, Moore KR, Blakely RD. Sodium-dependent norepinephrine-induced currents in norepinephrine-transporter-transfected HEK-293 cells blocked by cocaine and antidepressants. *J Exp Biol.* 1995;198(Pt 10):2197-2212.
220. Spencer CM, Wilde MI. Milnacipran: a review of its use in depression. *Drugs.* 1998;56:405-427.
221. Shuto S, Takada H, Mochizuki D, et al. (+/-)-(Z)-2-(aminomethyl)-1-phenylcyclopropanecarboxamide derivatives as a new prototype of NMDA receptor antagonists. *J Med Chem.* 1995;38:2964–2968.
222. Brannon GE, Stone KD. The use of mirtazapine in a patient with chronic pain. *J Pain Symptom Manage.* 1999;18:382-385.
223. Livingston MG, Livingston HM. Monoamine oxidase inhibitors. An update on drug interactions. *Drug Saf.* 1996;14:219-227.

224. Krishnan KRR. Monoamine oxidase inhibitors. In: Schatzberg AF, Nemeroff CB, eds. *Textbook of Psychopharmacology.* 2nd ed. Washington, DC: American Psychiatric Press, Inc.; 1998:239-249.
225. Menkes DB, Fawcett JP, Busch AF, Jones D. Moclobemide in chronic neuropathic pain: preliminary case reports. *Clin J Pain.* 1995;11:134-138.
226. Ginsberg F, Joos E, Geczy J, Bruhwyler J, Vandekerckhove K, Famaey JP. A pilot randomized placebo-controlled study of pirlindole in the treatment of primary fibromyalgia. *J Musculoskeletal Pain.* 1998;6:5-17.
227. Duale C, Raboisson P, Molat JL, Dallel R. Systemic morphine reduces the wind-up of trigeminal nociceptive neurons. *Neuroreport.* 2001;12:2091-2096.
228. Besse D, Lombard MC, Zajac JM, Roques BP, Besson JM. Pre- and postsynaptic distribution of mu, delta and kappa opioid receptors in the superficial layers of the cervical dorsal horn of the rat spinal cord. *Brain Res.* 1990;521:15-22.
229. Fields HL, Vanegas H, Hentall ID, Zorman G. Evidence that disinhibition of brain stem neurons contributes to morphine analgesia. *Nature.* 1983;306:684-686.
230. Yaksh TL, Hua XY, Kalcheva I, Nozaki-Taguchi N, Marsala M. The spinal biology in humans and animals of pain states generated by persistent small afferent input. *Proc Natl Acad Sci USA.* 1999;96:7680-7686.
231. Bennett RM. Emerging concepts in the neurobiology of chronic pain: evidence of abnormal sensory processing in fibromyalgia. *Mayo Clin Proc.* 1999;74:385-398.
232. Russell IJ, Kamin M, Bennett R, Schnitzer T, Green J, Katz W. Efficacy of tramadol in treatment of pain in fibromyalgia. *J Clin Rheumatol.* 2000;6:250-257.
233. Harati Y, Gooch C, Swenson M, et al. Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy. *Neurology.* 1998;50:1842-1846.
234. Rojas-Corrales MO, Gibert-Rahola J, Mico JA. Tramadol induces antidepressant-type effects in mice. *Life Sci.* 1998;63:PL175-PL180.
235. Rojas-Corrales MO, Ortega-Alvaro A, Gibert-Rahola J, Roca-Vinardell A, Mico JA. Pindolol, a beta-adrenoceptor blocker/5-hydroxytryptamine(1A/1B) antagonist, enhances the analgesic effect of tramadol. *Pain.* 2000;88:119-124.
236. Thomas RJ. Excitatory amino acids in health and disease. *J Am Geriatr Soc.* 1995;43:1279-1289.
237. Tremont-Lukats IW, Megeff C, Backonja MM. Anticonvulsants for neuropathic pain syndromes: mechanisms of action and place in therapy. *Drugs.* 2000;60:1029-1052.
238. Czuczwar SJ, Patsalos PN. The new generation of GABA enhancers: potential in the treatment of epilepsy. *CNS Drugs.* 2001;15:339-350.
239. Rowbotham M, Harden N, Stacey B, Bernstein P, Magnus-Miller L. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. *JAMA.* 1998;280:1837-1842.
240. Backonja MM. Gabapentin monotherapy for the symptomatic treatment of painful neuropathy: a multicenter, double-blind, placebo-controlled trial in patients with diabetes mellitus. *Epilepsia.* 1999;40(suppl 6):S57-S59.
241. McCleane GJ. Lamotrigine in the management of neuropathic pain: a review of the literature. *Clin J Pain.* 2000;16:321-326.
242. Martinez-Salio A, Porta-Etessam J, Berbel-Garcia A, Garcia-Morales I, de la Pena-Mayor P, Vicente-Fatela L. Antiepileptic drugs and neuropathic pain (in Spanish). *Rev Neurol.* 2001;32:345-350.
243. Conner GS. Efficacy of the antiepileptic topiramate in treatment-resistant diabetic or idiopathic neuropathy. Poster presented at: 20th Annual Scientific Meeting of the American Pain Society; April 21, 2001; Phoenix, AZ.
244. Altshuler LL, Keck PE, Jr, McElroy SL, et al. Gabapentin in the acute treatment of refractory bipolar disorder. *Bipolar Disord.* 1999;1:61-65.
245. Caraceni A, Zecca E, Martini C, De Conno F. Gabapentin as an adjuvant to opioid analgesia for neuropathic cancer pain. *J Pain Symptom Manage.* 1999;17:441-445.
246. Werner MU, Perkins FM, Holte K, Pedersen JL, Kehlet H. Effects of gabapentin in acute inflammatory pain in humans. *Reg Anesth Pain Med.* 2001;26:322-328.
247. Houghton AK, Lu Y, Westlund KN. S-(+)-3-isobutylgaba and its stereoisomer reduces the amount of inflammation and hyperalgesia in an acute arthritis model in the rat. *J Pharmacol Exp Ther.* 1998;285:533-538.
248. Hill CM, Balkenohl M, Thomas DW, Walker R, Mathe H, Murray G. Pregabalin in patients with postoperative dental pain. *Eur J Pain.* 2001;5:119-124.
249. Corbin AE, Remmers AE, LaMoreaux L, Young JP, Foster JL, Poole RM. Pregabalin reduces pain in patients with postherpetic neuralgia. Poster presented at: 20th Annual Meeting of the American Pain Society; April 20, 2001; Phoenix, AZ.
250. Sharma U, Iacobellis D, Glessner C, et al. Two studies show pregabalin effectively relieves pain in patients with painful diabetic peripheral neuropathy (studies 1008-14/-29). Poster presented at: 19th Annual Meeting of the American Pain Society; November 3, 2000; Atlanta, GA.

251. Field MJ, Oles RJ, Lewis AS, McCleary S, Hughes J, Singh L. Gabapentin (neurontin) and S-(+)-3-isobutylgaba represent a novel class of selective antihyperalgesic agents. *Br J Pharmacol.* 1997;121:1513-1522.

252. Maneuf YP, Hughes J, McKnight AT. Gabapentin inhibits the substance P-facilitated K(+)-evoked release of [(3)H]glutamate from rat caudal trigeminal nucleus slices. *Pain.* 2001;93:191-196.

253. Maneuf YP, McKnight AT. Block by gabapentin of the facilitation of glutamate release from rat trigeminal nucleus following activation of protein kinase C or adenylyl cyclase. *Br J Pharmacol.* 2001;134:237-240.

254. Bryans JS, Wustrow DJ. 3-substituted GABA analogs with central nervous system activity: a review. *Med Res Rev.* 1999;19:149-177.

255. Sawynok J. GABAergic mechanisms of analgesia: an update. *Pharmacol Biochem Behav.* 1987;26:463-474.

256. Caccia MR. Clonazepam in facial neuralgia and cluster headache: clinical and electrophysiological study. *Eur Neurol.* 1975;13:560-563.

257. Smirne S, Scarlato G. Clonazepam in cranial neuralgias. *Med J Aust.* 1977;1:93-94.

258. Moldofsky H, Lue FA, Mously C, Roth-Schechter B, Reynolds WJ. The effect of zolpidem in patients with fibromyalgia: a dose ranging, double blind, placebo controlled, modified crossover study. *J Rheumatol.* 1996;23:529-533.

259. Citera G, Arias MA, Maldonado-Cocco JA, et al. The effect of melatonin in patients with fibromyalgia: a pilot study. *Clin Rheumatol.* 2000;19:9-13.

260. Korszun A, Sackett-Lundeen L, Papadopoulos E, et al. Melatonin levels in women with fibromyalgia and chronic fatigue syndrome. *J Rheumatol.* 1999;26:2675-2680.

261. Klerman EB, Goldenberg DL, Brown EN, Maliszewski AM, Adler GK. Circadian rhythms of women with fibromyalgia. *J Clin Endocrinol Metab.* 2001;86:1034-1039.

262. Wikner J, Hirsch U, Wetterberg L, Rojdmark S. Fibromyalgia: a syndrome associated with decreased nocturnal melatonin secretion. *Clin Endocrinol (Oxf).* 1998;49:179-183.

263. Webb SM. Fibromyalgia and melatonin: are they related? *Clin Endocrinol (Oxf).* 1998;49:161-162.

264. Kameyama T, Nabeshima T, Matsuno K, Sugimoto A. Comparison of alpha-adrenoceptor involvement in the antinociceptive action of tizanidine and clonidine in the mouse. *Eur J Pharmacol.* 1986;125:257-264.

265. Nabeshima T, Matsuno K, Sugimoto A, Kameyama T. Antinociceptive activity induced by tizanidine and alpha 2-adrenoreceptors. *Neuropharmacology.* 1987;26:1453-1455.

266. Bousquet P, Dontenwill M, Greney H, Feldman J. Imidazoline receptors in cardiovascular and metabolic diseases. *J Cardiovasc Pharmacol.* 2000;35(7 suppl 4):S21-S25.

267. Berry H, Hutchinson DR. Tizanidine and ibuprofen in acute low-back pain: results of a double-blind multicentre study in general practice. *J Int Med Res.* 1988;16:83-91.

268. Berry H, Hutchinson DR. A multicentre placebo-controlled study in general practice to evaluate the efficacy and safety of tizanidine in acute low-back pain. *J Int Med Res.* 1988;16:75-82.

269. Shimomura T, Awaki E, Kowa H, Takahashi K. Treatment of tension-type headache with tizanidine hydrochloride: its efficacy and relationship to the plasma MHPG concentration. *Headache.* 1991;31:601-604.

270. Fromm GH. Baclofen as an adjuvant analgesic. *J Pain Symptom Manage.* 1994;9:500-509.

271. Steardo L, Leo A, Marano E. Efficacy of baclofen in trigeminal neuralgia and some other painful conditions: a clinical trial. *Eur Neurol.* 1984;23:51-55.

272. Fromm GH, Terrence CF, Chattha AS. Baclofen in the treatment of trigeminal neuralgia: double-blind study and long-term follow-up. *Ann Neurol.* 1984;15:240-244.

273. Wolf H. Preclinical and clinical pharmacology of the 5-HT3 receptor antagonists. *Scand J Rheumatol Suppl.* 2000;113:37-45.

274. Hamon M, Gallissot MC, Menard F, Gozlan H, Bourgoin S, Verge D. 5-HT3 receptor binding sites are on capsaicin-sensitive fibres in the rat spinal cord. *Eur J Pharmacol.* 1989;164:315-322.

275. Saria A, Javorsky F, Humpel C, Gamse R. 5-HT3 receptor antagonists inhibit sensory neuropeptide release from the rat spinal cord. *Neuroreport.* 1990;1:104-106.

276. Sawynok J, Reid A. Interactions of descending serotonergic systems with other neurotransmitters in the modulation of nociception. *Behav Brain Res.* 1996;73:63-68.

277. Farber L, Stratz T, Bruckle W, et al. Efficacy and tolerability of tropisetron in primary fibromyalgia: a highly selective and competitive 5-HT3 receptor antagonist. German Fibromyalgia Study Group. *Scand J Rheumatol Suppl.* 2000;113:49-54.

278. Haus U, Varga B, Stratz T, Spath M, Muller W. Oral treatment of fibromyalgia with tropisetron given over 28 days: influence on functional and vegetative symptoms, psychometric parameters and pain. *Scand J Rheumatol Suppl.* 2000;113:55-58.

279. Hocherl K, Farber L, Ladenburger S, et al. Effect of tropisetron on circulating catecholamines and other putative biochemical markers in serum of patients with fibromyalgia. *Scand J Rheumatol Suppl.* 2000;113:46-48.

280. Muller W, Stratz T. Results of the intravenous administration of tropisetron in fibromyalgia patients. *Scand J Rheumatol Suppl.* 2000;113:59-62.
281. Papadopoulos IA, Georgiou PE, Katsimbri PP, Drosos AA. Treatment of fibromyalgia with tropisetron, a 5HT3 serotonin antagonist: a pilot study. *Clin Rheumatol.* 2000;19:6-8.
282. Samborski W, Stratz T, Lacki JK, Klama K, Mennet P, Muller W. The 5-HT3 blockers in the treatment of the primary fibromyalgia syndrome: a 10-day open study with Tropisetron at a low dose. *Mater Med Pol.* 1996;28:17-19.
283. Fisher K, Coderre TJ, Hagen NA. Targeting the N-methyl-D-aspartate receptor for chronic pain management. Preclinical animal studies, recent clinical experience and future research directions. *J Pain Symptom Manage.* 2000;20:358-373.
284. Sorensen J, Bentgtsson A, Backman E. Pain analysis in patients with fibromyalgia: effects of intravenous morphine, lidocaine, and ketamine. *Scand J Rheumatol.* 1995;24:360-365.
285. Graven-Nielsen T, Aspegren Kendall S, Henriksson KG, et al. Ketamine reduces muscle pain, temporal summation, and referred pain in fibromyalgia patients. *Pain.* 2000;85:483-491.
286. McQuayHJ, Carroll D, Jadad AR, et al. Dextromethorphan for the treatment of neuropathic pain: a double-blind randomized controlled crossover trial with integral n-of-1 design. *Pain.* 1994;59:127-133.
287. Nelson KA, Park KM, Robinovitz E, Tsigos C, Max MB. High-dose oral dextromethorphan versus placebo in painful diabetic neuropathy and postherpetic neuralgia. *Neurology.* 1997;48:1212-1218.
288. Clark SR, Bennett RM. Supplemental dextromethorphan in the treatment of fibromyalgia: a double-blind, placebo-controlled study of efficacy and side-effects. *Arthritis Rheum.* 2000;43:S333.
289. Ferraccioli G, Guerra P, Rizzi V, et al. Somatomedin C (insulin-like growth factor 1) levels decrease during acute changes of stress related hormones: relevance for fibromyalgia. *J Rheumatol.* 1994;21:1332-1334.
290. Bennett RM, Clark SR, Campbell SM, Burckhardt CS. Low levels of somatomedin C in patients with the fibromyalgia syndrome. A possible link between sleep and muscle pain. *Arthritis Rheum.* 1992;35:1113-1116.
291. Bennett RM, Clark SC, Walczyk J. A randomized, double-blind, placebo-controlled study of growth hormone in the treatment of fibromyalgia. *Am J Med.* 1998;104:227-231.
292. Cuneo RC, Salomon F, Wiles CM, Hesp R, Sonksen PH. Growth hormone treatment in growth hormone-deficient adults. II. Effects on exercise performance. *J Appl Physiol.* 1991;70:695-700.
293. Cuneo RC, Salomon F, Wiles CM, Hesp R, Sonksen PH. Growth hormone treatment in growth hormone-deficient adults. I. Effects on muscle mass and strength. *J Appl Physiol.* 1991;70:688-694.
294. Almqvist O, Thoren M, Saaf M, Eriksson O. Effects of growth hormone substitution on mental performance in adults with growth hormone deficiency: a pilot study. *Psychoneuroendocrinology.* 1986;11:347-352.
295. McGauley GA, Cuneo RC, Salomon F, Sonksen PH. Psychological well-being before and after growth hormone treatment in adults with growth hormone deficiency. *Horm Res.* 1990;33(suppl 4):52-54.
296. Epstein SA, Kay G, Clauw D, et al. Psychiatric disorders in patients with fibromyalgia: a multicenter investigation. *Psychosomatics.* 1999;40:57-63.
297. Vgontzas AN, Bixler EO, Lin HM, et al. Chronic insomnia is associated with nyctohemeral activation of the hypothalamic-pituitary-adrenal axis: clinical implications. *J Clin Endocrinol Metab.* 2001;86:3787-3794.
298. Birmaher B, Heydl P. Biological studies in depressed children and adolescents. *Int J Neuropsychopharmacol.* 2001;4:149-157.

Not For Reprint

Organization IC1600 Bldg/Room REMSEN
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
If Undeliverable Return in Ten Days

OFFICIAL BUSINESS
PENALTY FOR PRIVATE USE, $300

AN EQUAL OPPORTU

U.S. OFFICIAL MAIL
$ 04.05⁰
MAILED FROM ZIP CODE

RETURNED TO SENDER

RECEIVED
FEB 28 2007
USPTO MAIL CENTER